RATIONALE FOR THE DEVELOPMENT OF ONTARIO AIR STANDARDS FOR *n*-HEXANE

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Standards Development Branch
Ontario Ministry of the Environment

Ontario

Executive Summary

The Ontario Ministry of the Environment (MOE) has identified the need to develop and/or update air quality standards for priority contaminants. The Ministry's Standards Plan, which was released in October, 1996 and revised in October, 1999, identified candidate substances for which current air standards will be reviewed over the next several years. *n*-Hexane was identified as a priority compound for review based on its pattern of use in Ontario and recent toxicological information that was published subsequent to the development of the existing guideline in 1976. A review of scientific and technical information relevant to setting an ambient air quality standard for *n*-hexane has previously been provided to stakeholders for their comments. This document provides the rationale for recommending an Ambient Air Quality Criterion (AAQC) and a half-hour Point of Impingement (POI) standard for *n*-hexane.

n-Hexane (CAS # 110-54-3) is a clear, colourless, highly volatile liquid. It has a faint odour and an odour threshold of 458 mg/m^3. *n*-Hexane is used in various industrial processes as a solvent such as in vegetable oil extraction, coatings, paints, rubber polymerization, and adhesives. *n*-Hexane is also used in low-temperature thermometers, and in the manufacturing of pharmaceuticals and other products.

n-Hexane is absorbed rapidly through the lungs after inhalation and is distributed throughout the body. Most of the absorbed *n*-hexane is subsequently excreted, unchanged, in exhaled air, although some is excreted as metabolites in both exhaled air and urine. Symptoms of exposure to *n*-hexane include sensorimotor polyneuropathy, cranial neuropathy, visual disturbances, dizziness, headaches, and fatigue. In animals, the peripheral and central nervous systems, and the male reproductive system are affected by *n*-hexane exposure. The neuropathological effect of *n*-hexane may be potentiated by methyl ethyl ketone. There are limited data on the carcinogenic potential of *n*-hexane.

Environment Canada has monitored ambient air levels for *n*-hexane from January 1993 to December 1995 from thirty-nine monitoring stations across Canada. From 4,233 samples nation-wide a mean concentration of 2.03 ± 2.87 μg/m^3 was obtained, with sampled concentrations ranged from no detection (detection limit of 0.1 μg/m^3) to a maximum of 35.26 μg/m^3. In Ontario, a range of 0.02 to a maximum of 110 μg/m^3 of *n*-hexane was detected from 1994 to 1996. The highest concentrations monitored were in the vicinity of Sarnia in 1994 (110 μg/m^3), and an asphalt plant in Vineland in 1996 (95 μg/m^3).

Ontario currently has an AAQC for *n*-hexane. The half-hour POI guideline is 35,000 μg/m^3 and the 24-hour AAQC is set at 12,000 μg/m^3. These criteria have been established on the basis of health effects.

In revising the air quality standards for Ontario, the Ministry of the Environment is considering risk assessments, and standards and guidelines developed by the US EPA, the States of California, New York, New Jersey, Michigan, and the Commonwealth of Massachusetts, the World Health Organization, The Netherlands, the Swedish Institute of Environmental Medicine and the Canadian Federal Government.

Of these, the US EPA, the states of Michigan, New Jersey, New York and California have developed (or are proposing to develop) criteria for *n*-hexane. The Commonwealth of Massachusetts, has developed criteria for alkanes/alkenes in general, of which *n*-hexane may be a constituent (not to exceed 25% by proportion). The US EPA has developed a Reference Concentration (RfC) of 200 µg/m^3 for *n*-hexane. This RfC is based on an epidemiological study of neurotoxic effects (functional impairment of the peripheral nervous system in several test items) in humans for occupational settings.

Following the recommendations by stakeholders, the Ministry has re-evaluated the toxicological information of *n*-hexane provided by these stakeholders and from a research of recent literature, and has also reviewed the comments provided by the Science Advisor Board on the RfC for this compound. The Ministry recommends the following AAQC and POI standard for *n*-hexane:

- **2,500 µg/m^3 (microgramme per cubic metre of air; 24-hour averaging time) based on health effects;**

- **7,500 µg/m^3 (half-hour averaging time) based on health effects.**

The Ministry welcomes comments from stakeholders on the revision of the proposed air quality standards and possible implementation issues.

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1.0 Introduction

Ontario regulates air emissions in order to achieve and maintain air quality which is protective of human health and the environment. The *Environmental Protection Act* (Section 9) requires that all stationary sources that emit, or have the potential to emit, a contaminant obtain a Certificate of Approval which outlines the conditions under which the facility can operate.

The Ministry of the Environment uses a combination of regulated point of impingement (POI) standards and point of impingement guidelines in reviewing Certificates of Approval (MOEE, 1994a), each of which is derived by mathematical scaling, from an ambient air quality criterion (AAQC). Ambient Air Quality Criterion (AAQCs) represent human health or environmental effect-based values, and are normally set at a level not expected to cause adverse effects based on continuous exposure. As such, economic factors, such as technical feasibility and costs, are not explicitly considered when establishing AAQCs.

All sources are required to comply with the Point of Impingement standards that are included in the schedule of Regulation 346. The regulation (Section 5(3)) specifies that a source cannot, "cause or permit the concentration of a contaminant at a point of impingement to exceed the standard prescribed in Schedule 1". All sources are required to comply with the standards in Regulation 346 unless they are specifically exempt. The concentration of a contaminant at a POI may be calculated in accordance with the Appendix of Regulation 346 (Air Dispersion Models).

In addition to POI standards established under Regulation 346, the Ministry also has a large number of POI guidelines. These are used by the Ministry to assess general air quality, and the *likelihood* of causing adverse effect (MOEE, 1994a). Like the POI standards specified in Regulation 346, POI guidelines are used in reviewing applications for Certificates of Approval, to approve new and modified emission sources. Once incorporated into a legal instrument such as a Certificate of Approval, POI guidelines are legally binding.

The Ontario Ministry of the Environment has identified the need to develop and/or update air guidelines/standards for priority toxic contaminants. The Ministry's Standards Plan, which was released in October, 1996 and revised in October, 1999 (MOEE, 1996; MOE, 1999a), identified 70 high priority substances for which current air standards will be reviewed, over the next several years. Factors used by the Ministry to determine which contaminants require priority include potential degree of exposure, volume of use, toxicity, Federal/Provincial commitments and sensitive sub-populations, including children.

All high priority substances will be standards (as opposed to guidelines) and will be in Schedule 1 of Regulation 346. In March 1998, following the 1996 initiative, the Ministry proposed a multi-step process for developing air quality standards (MOE, 1998). As an initial step, risk assessment and risk management information, relevant to establishing a standard for a particular

compound, was documented and made available for stakeholder review. This provided stakeholders with the opportunity to critically review the information and provide any additional information they felt should be considered by the Ministry in setting an air quality standard for a particular compound.

In assessing the available information for a substance, when the Ministry believes that meeting the proposed standard immediately will not be possible due to implementation issues related to economics, technical feasibility and the time needed to establish appropriate control technology, the Ministry will propose a range of values within which an interim standard will be set. This range of values is based on the following considerations:

- For carcinogens, the interim standard will be set within a range of air concentrations which corresponds to a risk level of 1 excess cancer in a population of 1,000,000 (10^{-6}) over a lifetime up to, but no higher than, 1 excess cancer in a population of 10,000 (10^{-4}) over a lifetime and;

- For non-carcinogens, the range under consideration for the interim standard is from the proposed POI standard up to 10 times this proposed standard. In cases where the reduction in the standard for a non-carcinogen is less than 10-fold overall, the upper end of the range for the interim standard is selected at a value which at least 90% of facilities in Ontario are anticipated to be able to presently meet based on MOE's records of emissions and modelled ground level concentrations.

The interim standard which is ultimately selected will be considered a first step in a ramping down process to a final standard. The final POI standard will be the lower number of the range from which the interim standard is selected. The ramping down characteristics, including an appropriate timeframe, will be discussed with stakeholders as part of the detailed risk management phase which will be undertaken by the Ministry subsequent to this posting. An interim standard will constitute the POI standard in force until such time it is revised through the risk management process.

n-Hexane was identified as a priority for review based on its pattern of use in Ontario and recent toxicological information published subsequent to the development of the existing standards in 1976. A review of scientific and technical information relevant to setting an ambient air quality standard for *n*-hexane had been provided in a previous document for stakeholder comments (MOE, 1999b). This document provides the rationale for recommending an Ambient Air Quality Criterion (AAQC) and a half-hour point of impingement (POI) standard for *n*-hexane.

2.0 General Information

2.1 Physical and Chemical Properties

The following list provides some general information on *n*-hexane and its properties:

CAS #	110-54-3
RTECS #	MN9275000
UN #	1208
Conversion Factors	1 ppm = 3.52 mg/m^3 @ 25 °C and 760 mm Hg 1 mg/m^3 = 0.284 ppm @ 25 °C and 760 mm Hg
Boiling Point	69 °C
Flash Point	-21.7 °C
Henry's Law Constant	Range of 50,586 - 190,000 Pa m^3/mol
Log K_{OW}	3.9
Formula	C_6H_{14}
Molecular Weight	86.2 g/mol
Vapour Density (air = 1)	2.97
Vapour Pressure	150 mm @ 25 °C
Common Synonyms	*n*-hexane, hexyl hydride, Skellysolve B

n-Hexane is a clear, colourless, highly volatile liquid with a faint odour (Lewis, 1991; WHO, 1991). An odour threshold for *n*-hexane has been reported to be 458 mg/m^3 (ACGIH, 1991). It is poorly soluble in water and soluble in most organic solvents, including ethanol and ether (ACGIH, 1991; WHO, 1991). Purified *n*-hexane consists of 95-99.5% *n*-hexane with small amounts of other *n*-hexane isomer impurities (WHO, 1991). Commercial-grade hexane consists of a mixture of *n*-hexane isomers as well as cyclopentane, cyclohexane, pentane, and heptane (ACGIH, 1991; WHO, 1991). Hexane may comprise from 20-80% of commercial *n*-hexane (ACGIH, 1991; WHO, 1991).

2.2 Uses of *n*-Hexane

Commercial hexane is used in various industrial processes, including, as a solvent in vegetable oil extraction, coatings, paints, rubber polymerization, and adhesives (ACGIH, 1991; WHO, 1991). *n*-Hexane is also used as a laboratory chemical, in low-temperature thermometers, and in the manufacture of pharmaceuticals and other products (WHO, 1991).

2.3 Sources and Levels

n-Hexane occurs naturally in natural gas and crude oil. It is also produced industrially. *n*-Hexane is not listed in Environment Canada's National Pollutant Release Inventory for environmental release reporting by the industries (NPRI, 1997).

Environment Canada has ambient air data for *n*-hexane levels from January 1993 to December 1995 from thirty-nine monitoring stations across Canada. From 4,233 samples, a mean concentration of 2.03 ± 2.87 $\mu g/m^3$ was observed. The reported concentrations ranged from no detection (detection limit of 0.1 $\mu g/m^3$) to a maximum of 35.26 $\mu g/m^3$ (Environment Canada, 1997).

In Ontario between1994 to 1996, unscheduled monitoring results indicate that the half-hour average concentrations for *n*-hexane varied from 0.02 $\mu g/m^3$ (the detection limit) to a maximum of 110 $\mu g/m^3$. The highest concentrations monitored were in the vicinity of Sarnia in 1994 (110 $\mu g/m^3$) and in Vineland in 1996 (95 $\mu g/m^3$) (MOEE, 1997). In two separate special monitoring surveys performed in 1997, the average and maximum half-hour concentrations down-wind from a facility at Sarnia were 9 and 64 $\mu g/m^3$, respectively. At another site in the Greater Toronto Area, the average and maximum half-hour concentrations down-wind from a facility were 5 and 19 $\mu g/m^3$, respectively (MOE, 1998b). Recent monitoring data provided by the Lambton Industrial Society, indicated that a general down trend was observed in the annual average concentrations for *n*-hexane from 1994 to 1998 in Sarnia (6.9 to 3.4 $\mu g/m^3$) and Corunna (4.3 to 1.8 $\mu g/m^3$) (LIS, 1999). No consistent pattern for the maxima was observed; the maxima values ranged from 49.2 $\mu g/m^3$ in 1995 to 8.4 $\mu g/m^3$ in 1997 in Sarnia and from 24.1 in 1994 to 7.8 in 1997 in Corunna. The maximum hourly averages in Sarnia between 1995 and 1996 were 154 to 380 $\mu g/m^3$ (detection limit was 0.64 $\mu g/m^3$) (LIS, 1997).

From an analysis of recent applications for Certificates of Approval in Ontario, a sample of 32 facilities with emissions of *n*-hexane covered by a Certificate was identified. These approvals were for emissions from a variety of industries in pharmaceuticals, food packaging, automotive products, plastic and metal products, petroleum products and chemical products. The median Ground Level Concentration (GLC) estimated by Regulation 346 dispersion modelling for all 32 sources was approximately 32 $\mu g/m^3$. The maximum and minimum were 3601 and 0.024$\mu g/m^3$, respectively.

2.4 Environmental Fate

Most transport of *n*-hexane occurs in the vapour phase after emission into the environment since its water solubility is very low (9.5 mg/L at 25 °C). *n*-Hexane is not expected to affect the physical properties of the atmosphere, to deplete the ozone layer, or to alter precipitation patterns. The rate constant for the reaction of hydroxyl radicals with *n*-hexane ranges from 5.63

x 10^{-12} to 6.2 x 10^{-12} cm^3/sec (WHO, 1991). Based on degradation by hydroxyl radicals alone, the half-life of *n*-hexane in the troposphere is estimated to be 2 to 2.4 days (WHO, 1991). Similar hydrocarbons undergo the conversion to form smog, but *n*-hexane is one of the least photochemically reactive hydrocarbons (WHO, 1991)

3.0 Toxicology of *n*-Hexane

The following toxicological review of *n*-hexane is primarily focussed on the inhalation route of exposure since this is the predominant route of human exposure. Data on other exposure media are included where relevant or where inhalation data is lacking.

n-Hexane is absorbed rapidly through the lungs after inhalation exposure and is distributed throughout the body. Most of the absorbed *n*-hexane is metabolized to a number of substances which have been identified in the urine of workers exposed to *n*-hexane, including 2,5-hexanedione (considered to be the neurotoxic agent), 2,5-dimethylfuran, γ-valerolactone, and some 2-hexanol (WHO, 1991; ATSDR, 1997). Approximately 10-20% of *n*-hexane absorbed through inhalation is excreted unchanged in the exhaled air. In rats, 2-hexanol was the major metabolite identified in the urine during urine collection and accounted for about 60 - 70% of total metabolites collected (WHO, 1991; ATSDR, 1997). The main target organ of *n*-hexane is the nervous system.

3.1 Acute Toxicity

Effects of acute exposure to *n*-hexane in humans include irritation to the eyes, nose, and throat, blurred vision, and neurotoxicity at relatively high concentrations. Inhalation of *n*-hexane at 7,040 mg/m^3 for 10 minutes did not induce any neurobehavioural symptoms, whereas exposure to 17,600 mg/m^3 for 10 minutes resulted in vertigo and giddiness (ACGIH, 1991; WHO, 1991). Drowsiness was observed as a result of exposure to *n*-hexane concentrations of 3,520 to 89,760 mg/m^3 for 30-60 minutes (WHO, 1991). Volunteers exposed to *n*-hexane vapour at 1,760 mg/m^3 for 3-5 minutes did not experience eye irritation (WHO, 1991).

n-Hexane has low toxicity to animals in acute exposures. A 1-hour inhalation LC_{50} of 271,040 mg/m^3 (77,000 ppm) has been observed in male Fischer rats (WHO, 1991). Mice exposed to *n*-hexane at concentrations above 133,760 mg/m^3 (38,000 ppm) showed loss of postural reflexes followed by death. Ataxia and decreased motor activity were noted in Sprague-Dawley rats following exposures to *n*-hexane at concentrations between 302,720 to 316,800 mg/m^3 (86,000 - 90,000 ppm) for 25 to 30 minutes. Rats exposed to 84,480 mg/m^3 (24,000 ppm) *n*-hexane for 10 minutes did not showed any behavioural effects. Histopathological changes of the lung tissues (lamellar inclusions in type II pneumocytes) were noticed in Wistar rats exposed to *n*-hexane at 35,200 mg/m^3 (10,000 ppm) for 4 or 8 hours or to 24,640 mg/m^3 (7,000 ppm) for 8 hours; there

were no effects in intrapulmonary nerves. *n*-Hexane appears to be toxic to the male reproductive system. Testicular lesions, degeneration of the primary spermatocytes and mild exfoliation of spermatids, were observed in Sprague Dawley rats exposed to 17,600 mg/m^3 (5000 ppm) for 24 hours. Rats recovered completely 30 days after the cessation of treatment.

3.2 Subchronic and Chronic Toxicity

Case studies of occupational exposure to *n*-hexane show that exposure for intermediate (15 to 365 days) and long (over one year) periods of time results in peripheral neuropathy (degeneration of nerve endings) in humans (ATSDR, 1997). The ATSDR has established a minimum risk level for chronic inhalation exposure of 0.6 ppm or 2,100 µg/m^3. This was derived from a study of workers exposed to approximately 58 ppm (210,000 µg/m^3) for an average of 6 years.

The most frequently observed adverse effects of long-term exposure to *n*-hexane in humans are sensorimotor polyneuropathy, cranial neuropathy, blurred vision, and abnormal colour vision (as reviewed in US EPA, 1998, in ATSDR, 1997 and in WHO, 1991). Symmetrical paraesthesia and weakness are the first few signs of *n*-hexane neuropathy, with the lower extremities usually affected first. Also accompanying neuropathy is a marked reduction in conduction velocity in sensory and motor nerves. Nerve biopsy showed axonal lesions of the large myelinated fibres with axonal swellings followed by myelin retraction at the node of Ranvier. There was only a mild to moderate reduction in the number of fibres, mainly of large myelinated fibres. The small myelinated or unmyelinated fibres were seldom affected. Muscle biopsy indicated signs of myofibrillar atrophy. Recovery from neuropathy is gradual and slow and residual neuropathy may persist for a few years. Headache, anorexia, and dizziness, muscular weakness, blurred vision, and fatigue may precede or coincide with the neuropathy. Clinical examination indicated that reduced body weight and decreased or absent reflexes were noticeable (WHO, 1991). Neuropathy has been reported to occur at exposure concentrations ranging from 97 to 8,125 mg/m^3 (30 to 2500 ppm), and overt neuropathy may be observed only after two months to five years of exposure (WHO, 1991). Cases of polyneuropathy have been reported in workplaces where *n*-hexane was used as; a mixing solvent in tungsten carbide milling, as a glue solvent in vinyl sandal making, as a machine cleansing agent in press proofing, or with other solvents in shoe manufacturing (WHO, 1991; ATSDR, 1997).

Sanagi *et al.* (1980, as cited in WHO, 1991; US EPA, 1998 & ATSDR, 1997), carried out an epidemiological study on two age-matched groups of workers at a tungsten carbide alloy factory to investigate the neurotoxicity of *n*-hexane. *n*-Hexane was used in the production of tungsten carbide alloys. Fourteen workers under 50 years of age, who worked in ball milling and drying of tungsten carbide alloy operations, were studied. The exposure durations ranged from 1 to 12 (mean: 6.2) years. The control group used consisted of 14 workers from the sintering workshop, who were not exposed to *n*-hexane. The mean concentration of *n*-hexane, for the 8-hour time-weighted-average exposure period over a 2-years, was 204 mg/m^3 (58 ppm). The average

concentrations for acetone in the workplace ranged from 52 - 164 mg/m^3 (22 - 69 ppm). Clinical and electro-physiological examinations were performed in this study.

In the exposed group, headache, hyperaesthesia (abnormal acuteness of sensation of touch or pain) in the limbs and muscle weakness were reported most often. Paraesthesia (abnormal sensation of burning, tickling or tingling) was reported in three exposed workers and one control worker. A slightly higher prevalence of diminished bicipital and patellar tendon reflexes was observed in the exposed group. Significant effects on muscle strength (jump test on one foot) and vibration sensation (tuning fork) were noted in the exposed group. There were no abnormalities identified in the cranial nerves, the pyramidal tract or peripheral motor nerves. Electro-physiological examination did not reveal any neuropathy in any worker, but in the exposed group, the mean maximal motor conduction velocities in the posterior tibial nerve were significantly reduced as compared with those in the control group. Moreover, the mean distal latency of the posterior tibial nerve was significantly increased in the exposed group. These observations were consistent with the *n*-hexane-induced peripheral neuropathy observed in animals. The US EPA identified a LOAEL of 58 ppm (204 mg/m^3) for neurological effects in this study (Sanagi *et al.*, 1980). This LOAEL was based on an 8-hour time-weighted-average for occupational exposure and was adjusted to a value of 73 mg/m^3 for continuous exposure in the general population.

Similar neuropathological effects of *n*-hexane were also observed in animals (as reviewed in WHO, 1991 and ATSDR, 1997). The sequence of events in neuropathy in rats has been detailed. The first sign of neuropathy appears to begin with an increase in the number of 10 nm axonal filaments, and the accumulation of swellings on the proximal side of the nodes of Ranvier in the distal regions of large myelinated fibres. With continuous exposures, a retrograde spread of axonal swellings up the nerve occur, and smaller myelinated and unmyelinated fibres may became involved. The nerve terminal is unaffected until later in the process. The enlarged axons displace the paranodal myelin sheaths leaving denuded swellings in areas near the nodes of Ranvier. This process occurs before functional impairment is evident and can be reversed on cessation of exposure. When exposure ceases, swelling diminishes and proliferation of Schwann cells occurs at these sites with subsequent remyelination of the axons. With continuous exposure to *n*-hexane, axonal restoration and remyelination do not occur at all swellings, and the section of the nerve fibre between the swelling and the terminal undergoes breakdown. However, axonal spouting is often seen at the intact portion of a degenerated fibre even while intoxication continues. This regenerative process can re-establish motor and sensory function when intoxication ends.

The nerve fibres most vulnerable to *n*-hexane in rats were branches of the nerves innervating the muscles of the hind limbs (in the sequence of order: tibial nerves for the calf muscles, plantar nerves for the flexor digitorium brevis muscle and the sensory plantar nerves for the digits). When exposure continues, axonal degeneration may ascend the plantar and tibial nerves. The

most sensitive fibres appear to be the largest. It has been demonstrated that *n*-hexane, or its toxic metabolite, 2,5-hexanedione, can induce axonal swelling and degeneration in the central nervous system including the areas such as the medulla oblongata and the spinal cord.

Sprague-Dawley rats were exposed to *n*-hexane between 1408 - 2112 mg/m^3 (400 - 600 ppm) for 1 to 23 weeks. Axonal swellings were observed in the hind limb nerves (tibial and plantar nerves) and in the central nervous system (medulla oblongata and the spinal cord and the cerebellar vermis) and these occurred before the weakness of the hind limbs was noticed. Male CD rats were exposed to *n*-hexane at 440 or 1760 mg/m^3 (125 or 500 ppm) for 22 hours/day, 7 days/week. Axonal swelling was noticed in the tibial nerve and the medulla oblongata after 2 months of exposure to 1760 mg/m^3. After 6 months of exposure, pronounced degeneration and loss of axons in the tibial and sciatic nerves, the lumbar spinal cord and the medulla oblongata was observed. Recovery of these neuropathological effects noted at 1760 mg/m^3 (500 ppm) was complete by 6 weeks after the cessation of the treatment. Male Fischer-344 rats exposed to 3520 mg/m^3 (1000 ppm) *n*-hexane for 24 hours/day, 5 days/week for 11 weeks developed inhibition of spontaneous motor activity. Hind limb grip strength was diminished and the fore limb grip strength was less affected. Multi-sensory conditioned avoidance response and pole-climbing ability decreased after 8 weeks, but recovered between weeks 18 and 36. In two separate studies, exposure of rats to *n*-hexane at 440 mg/m^3 (125 ppm) for about 22 hours/day, 7 days/week for 26 to 34 week, did not induce observable clinical or histological peripheral or central neurotoxicity.

Tail nerve conduction velocity was reduced in male Wistar rats exposed to *n*-hexane at 3696 mg/m^3 (1050 ppm) for 12 hours/day, 7 days/week for 16 weeks. There was no definite clinical signs of neurotoxicity. Clinical signs of neurotoxicity were noticed when rats were exposed to 10560 mg/m^3 (3000 ppm). No significant effects on tail nerve conduction time in rats were observed following exposure to *n*-hexane at 373 mg/m^3 (106 ppm) for 12 hours/day, 7 days/week for 24 weeks; histological examination of one rat indicated that the tail nerve was normal. However, when rats were exposed to *n*-hexane at 722 or 1725 mg/m^3 (205 or 490 ppm) for 24 weeks, axonal swellings and demyelination were evident in the tail nerves at the concentration of 722 mg/m^3. A higher no-observed-effect-level was obtained from male Wistar rats exposed to *n*-hexane at 1795 mg/m^3 (510 ppm), using daily 8-hours exposures for 33 weeks; no effects on tail nerve structure or function were noted.

Sprague-Dawley rats of both sexes exposed to *n*-hexane up to 35200 mg/m^3 (10000 ppm) for 6 hours/day, 5 days/week for 13 weeks did not show changes in neurological functions (posture, gait, tone and symmetry of the facial muscles, pupillary reflexes, palpebral reflexes, extensor thrust, cross-extensor thrust). Isolated and greatly enlarged axons were noted in the medulla of one male rat in the 35200 mg/m^3 group; no other histopathological lesions were observed in the brain. Peripheral axonopathy of the tibial nerve was noticed in 4 of 5 male rats in the 35200 mg/m^3 group and 1 male in the 22880 mg/m^3 (6500 ppm) group. The lesions were at an early

stage of development and consisted of paranodal axonal swellings in nerve fibres. Segmental demyelination and axonal degeneration were not evident. No consistent changes were observed in any females or males from the 10560 mg/m^3 (3000 ppm) group.

It was also found that exposure of male Wistar rats to *n*-hexane at 2464 mg/m^3 (700 ppm) for 8 hours/day, 7 days/week for up to 40 week did not result in signs of clinical neurotoxicity. In contrast, male Wistar rats exposed to 1760 or 2464 mg/m^3 (500 or 700 ppm) *n*-hexane for 22 hours/day, 7days/week for 9 weeks showed signs of narcosis. Weakness in hind limbs of exposed animals developed, leading to paralysis, and eventually to quadriplegia. Complete hind limb paralysis was seen in the ninth week in the 1760 mg/m^3 group. Rats exposed to 2464 mg/m^3 developed hind limb paralysis in the fourth week of exposure. Histological examination indicated axonal swellings of the tibial nerve and portions of the ischiatic nerve. Breakdown of the axons and demyelination were observed distal to the swellings. Axonal swellings were also evident in the spinal cord near the cervical region. It would appear that the development of neuropathy may be related to whether exposures to *n*-hexane are intermittent (6 - 8 hours/day) or continuous (22 - 24 hours/day), however, this needs to be studied further.

In one study, B6C3F mice were exposed to *n*-hexane at 0, 1760, 3520, 14080 and 35200 mg/m^3 (0, 500, 1000, 4000 and 10000 ppm) for 6 hours/day, 5 days/week for 13 weeks. In addition, mice were also exposed to 3520 mg/m^3 for 22 hours/day, 5 days/week for 13 weeks. The only neurobehavioural effect observed was a decrease in locomotor activity in female mice exposed to 35200 mg/m^3 for 6 hours/day. At this concentration, paranodal swellings were not noted in the control mice, but swellings of the tibial nerves were observed in 3 out of 4 male and 3 out of 4 female mice. In the treatment group of 3520 mg/m^3 for 22 hours/day, similar paranodal swellings were observed. The severity of the lesion was mild and no segmental demyelination, distal axon degeneration or axonal swellings in the spinal cord were noted. This insensitivity could be related to the relatively short length and smaller diameter of the myelinated axon, as compared to rats or humans (Dunnick *et al.*, 1989 as cited in US EPA, 1998 & ATSDR, 1997). In addition to the effects on axonal swelling, *n*-hexane exposure at 1000 ppm (3520 mg/m^3) also induced mild inflammatory, erosive and regenerative lesions in the olfactory and respiratory epithelia of the nasal cavity.

Inhaled *n*-hexane also induced other systemic effects such as mild inflammatory lesions of the nasal epithelium. In an animal study reported by Dunnick *et al.* (1989), subchronic inhalation of *n*-hexane was carried out by exposing male and female B6C3F$_1$ mice (10/sex/dose) to 0, 500, 1,000, 4,000, and 10,000 ppm (0, 1,762, 3,525, 14,099, and 35,247 mg/m^3, respectively) for 6 hours per day, 5 days per week for 13 weeks (duration adjusted exposure calculated as 0, 315, 629, 2,518, and 6,294 mg/m^3). An additional group of mice was exposed to 1,000 ppm (3,525 mg/m^3) for 22 hours per day, 5 days per week for 13 weeks (duration adjusted exposure calculated as 2,308 mg/m^3). Toxicity was assessed by examining both behavioral and physiological (e.g. body weight, organ weight, organ tissues, etc.) endpoints of toxicity.

Histopathological changes included mild inflammatory, erosive and regenerative lesions in the olfactory and respiratory epithelium of the nasal passages of the mice exposed to 2,308 mg/m^3 and greater. Multifocal regeneration and metaplasia in the olfactory epithelium were observed at 3525 mg/m^3. Minimal lesions were observed in the 315 and 629 mg/m^3 groups. Other neurohistopathological evidence of toxicity was observed in 6 of the 8 animals in the 2,309 mg/m^3 group and 6 of the 8 animals in the 6,294 mg/m^3 dose group, but not in 8 of the 10 animals in the control group.

3.3 Developmental and Reproductive Toxicity

Developmental or reproductive studies on humans were not available. *n*-Hexane does not appear to cause embryotoxic or teratogenic effects. Pregnant albino rats were exposed to 3,489 mg/m^3 *n*-hexane (99% pure) vapour for 6 hours/day during days 8 to 16 of gestation. Although significantly depressed postnatal growth was observed up to 3 weeks after birth, growth returned to normal by 7 weeks. No difference from controls was noted in fetal resorption, birth weight or other abnormalities (as reviewed in US EPA, 1998). *n*-Hexane vapour (99.9% purity) at concentrations of 0, 705, 3,525, or 17,623 mg/m^3 was administered to pregnant rats for 20 hours/day for 14 consecutive days from days 6 to 19 of gestation (as reviewed in US EPA, 1998). Maternal toxicity was indicated by reduction in weight gain in all exposure groups, but was statistically significant only at the highest concentration. There was no significant difference in the incidence of fetal malformations or other reproductive indicators, such as the number of implantations, the mean percent of live pups per litter, the mean percent of resorptions per litter, or the fetal sex ratio compared to controls. *n*-Hexane caused testicular damage in adult male Sprague-Dawley rats exposed to 3,525 mg/m^3 18 hours/day for 61 straight days. A total loss of the germ cell line in a fraction of the animals was observed up to 14 months post-exposure (as reviewed in US EPA, 1998). In contrast, no treatment-related reproductive effects were observed in the seminal vesicles, prostate, testis and epididymis of male Sprague-Dawley rats exposed to *n*-hexane at 1760 mg/m^3 (500 ppm) for 22 hours/day for 6 months (as reviewed in ATSDR, 1997). Similarly, no reproductive tissue lesions were noticed in male F-344 rats (in testis, seminal vesicles, prostate or epididymis) or in female rats (in ovaries, uterus, vagina, cervix) exposed to *n*-hexane at 10560, 22880 or 35200 mg/m^3 (3000, 6500, or 10000 ppm) for 6 hours/day, 5 days/week for 13 weeks (as reviewed in WHO, 1991 & ATSDR, 1997).

3.4 Genotoxicity

The limited mutagenicity testing conducted on *n*-hexane indicates little potential for genotoxicity (ATSDR, 1997). An *in vitro* study in which Chinese hamster ovary cells were exposed to undiluted liquid *n*-hexane in the absence of a metabolizing fraction resulted in chromosomal damage (as reviewed in WHO, 1991). There was no significant increase in point mutations in cultured mammalian cells or bacteria, nor DNA damage in bacteria as a result of *n*-hexane exposure (as reviewed in WHO, 1991). No increase in unscheduled DNA synthesis was found in

human lymphocytes *in vitro*. Chromatid breaks in rat bone marrow cells were reported in an *in vivo* study (as reviewed in WHO, 1991). *n*-Hexane did not induce dominant lethal mutations (for germ cell mutation test) in male CD-1 mice treated with 99 ppm (350 mg/m^3) or 396 ppm (1400 mg/m^3) *n*-hexane for 6 hours/day, 5 days/week for 8 weeks (as reviewed in ATSDR, 1997).

3.5 Carcinogenicity

There are limited data on the carcinogenic potential of *n*-hexane. Dermally applied, *n*-hexane did not result in the enhanced formation of skin tumours in mice after exposure to 7,12-dimethylbenzanthracene, a tumour initiator, or following co-exposure with croton oil, a promoting agent (WHO, 1991). Papillary tumours have been reported in bronchiolar epithelium of rabbits after 24 week exposure to 3,000 ppm (11,000 mg/m^3) (Lungarella *et al.*, 1984, as cited in ATSDR, 1997)

3.6 *n*-Hexane in Solvent Mixtures

Solvents in commercial applications, for example solvents in the glue used in the shoe manufacturing industry, often contain *n*-hexane and other solvents, such as methyl ethyl ketone (MEK), methylisobutyl ketone (MIBK) and toluene. There have been reports that some of these solvents may enhance the neurotoxic effect of *n*-hexane (ATSDR, 1997; WHO, 1991).

It has been suggested that MEK potentiates the neurotoxic effects of *n*-hexane. Two thousand cases of solvent abuse, which resulted severe polyneuropathy in Germany in 1974, led to research on the potential for MEK to enhance the adverse health effects of *n*-hexane, and on the interactions of MEK with other hexacarbon solvents (as reviewed in WHO, 1993 & ATSDR, 1997). Victims of solvent abuse often found development of paraesthesia and weakness in leg and arm muscles. Neurophysiological and histological findings indicated reduction in motor and sensory nerve conduction velocities and were in proportion to the degree of paresis. Damages to the nerves were also reported. The outbreak of neuropathy in solvent abuse victims coincided with the change of solvent formulation from one with *n*-hexane, benzene fraction, ethyl acetate and toluene to a similar solvent mixture with less (16%) *n*-hexane and the addition of 11% MEK. It was suggested that MEK potentiated the neuropathy of *n*-hexane.

Similar findings were obtained from animal studies. It has been demonstrated that the neurotoxicity of *n*-hexane is potentiated by methyl ethyl ketone (MEK) under continuous exposure conditions (as reviewed in US EPA, 1998 & ATSDR, 1997 and WHO, 1991). *n*-Hexane-induced hind limb paralysis and related neuropathy were manifested after 9 weeks in all 5 Wistar rats exposed continuously to *n*-hexane at 1,760 mg/m^3 (500 ppm), 22 hours/day, 7 days/week. These clinical signs were present 1 week earlier in animals exposed to mixtures of 1,056 mg/m^3 (300 ppm) *n*-hexane with 590 mg/m^3 (200 ppm) MEK and 1,408 mg/m^3 (400 ppm) *n*-hexane with 295 mg/m^3 (100 ppm) MEK. Exposure to 1,760 mg/m^3 *n*-hexane and 590 mg/m^3

MEK resulted in complete hind limb paralysis after 4 weeks. Rats exposed to *n*-hexane at 2464 mg/m^3 (700 ppm) or 1760 mg/m^3 *n*-hexane + 590 mg/m^3 (200 ppm) MEK for 8 hours/day, 7 days/week for 40 weeks did not showed clinical signs of neuropathy. It appears that MEK potentiated the neurotoxic effect of *n*-hexane (shortened onset of neuropathological effect of *n*-hexane) under continuous exposure conditions, but not under intermittent exposures.

Understanding the possible mode of action of hexacarbon solvents in inducing neuropathy may explain the likely mechanism of MEK in the potentiation of the neurotoxic effects of *n*-hexane. It has been postulated that *n*-hexane is oxidized by hepatic microsomal enzymes to 2,5-hexanedione, the proximate neurotoxicant. The 2,5-hexanedione formed may induce cross-linking of neurofilaments and this may result in the blocking of transport at the node of Ranvier. The accumulation of neurofilaments may induce swelling proximal to the nodes and may lead to axonal degeneration distal to the nodes. In animal studies it was found that if the concentrations or doses of *n*-hexane or 2,5-hexanedione were high enough and sustained for long enough periods of time, clinical signs of neural degeneration were evident and were made more severe, or the onset of neuropathy was often shortened by the co-exposure with MEK (WHO, 1991 & 1993). Although MEK potentiation of the neurotoxic effects of *n*-hexane has frequently been observed in rats *in vivo*[1], information on the mechanism of action for MEK has not been well described. There are some suggestions that MEK may have metabolic interactions with *n*-hexane (WHO, 1993). Simultaneous inhalation exposure of *n*-hexane and MEK resulted in lower levels of 2,5-hexanedione (a common metabolite of *n*-hexane) in urine of rats *in vivo* and initially lower, but later somewhat elevated, levels of 2,5-hexanedione in serum *in vivo*. However, the increased 2,5-hexanedione level alone cannot explained the potentiation of *n*-hexane neurotoxicity. It appears that MEK may be involved in the activation of some components in the metabolism of *n*-hexane. Pretreatment of rats with MEK prior to inhalation exposure to *n*-hexane resulted in higher levels of 2,5-hexanedione in several tissues, including blood (WHO, 1993). There are, as of yet, insufficient information to delineate the mechanism of MEK in enhanced hexacarbon solvent neurotoxicity. It may be of relevance to note that MEK has been demonstrated to potentiate the hepatotoxic effects of haloalkane solvents, such as carbon tetrachloride and chloroform, through a possible mechanism of increased bioactivation of haloalkanes.

3.7 Environmental Effects

There are a lack of data on the effects of *n*-hexane on terrestrial wildlife. Since *n*-hexane has low water solubility and is highly volatile, it is primarily found in air. The risk of exposure of aquatic organisms is likely to be low and transient except for uncontrolled discharges into surface waters. A few laboratory experiments have been conducted on the water flea, *Daphnia magna*, however

[1] For more information on the MEK potentiated neurotoxic effects of hexacarbon solvents and haloalkanes in animals, see WHO, 1993.

these experiments were static tests and the actual *n*-hexane concentration was not measured during the course of the experiment, resulting in LC_{50} values of >1,000 mg/L (Bringmann *et al*, 1982 as cited in WHO, 1991). Another experiment conducted on *Daphnia magna* in a closed, airtight container determined a 48-h LC_{50} of 3.9 mg/L, but does not represent natural environmental conditions where *n*-hexane will rapidly volatilize from water (Bobra *et al*, 1983 as cited in WHO, 1991).

4.0 Existing Air Quality Criteria

4.1 Overview

Ontario currently has AAQCs for *n*-hexane. The half-hour POI guideline is 35,000 $\mu g/m^3$ and the 24-hour AAQC is currently set at 12,000 $\mu g/m^3$. These criteria have been established on the basis of health effects (MOEE, 1994a).

The documentation from ten agencies, including, the United States federal government, the States of California, New York, New Jersey and Michigan, the Commonwealth of Massachusetts, the World Health Organization, the Netherlands, the Swedish Institute of Environmental Medicine and the Canadian Federal government, was reviewed for the existence and basis of air quality criteria for *n*-hexane. A brief summary of this review is presented in Table 1, and agency-specific summaries of information concerning air quality guidelines for *n*-hexane are presented in Section 11.0. In reviewing the air quality guidelines and exposure limits presented in Table 1, it should be noted that the Ministry of the Environment normally uses a factor of **15** to convert from criteria, based on annual average concentrations, to half-hour POI standards, and a factor of **3** to convert from criteria, based on 24-hour average concentrations. These factors are derived from empirical measurements and are selected to ensure that if the short-term limit is met, air quality standards based on longer-term exposures will not be exceeded (MOE, 1987; MOEE, 1994b). However, depending on the health end-point being considered, other conversion factors may also be employed.

None of the agencies reviewed considered *n*-hexane to be carcinogenic. Four agencies, the US EPA and the states of Michigan, New Jersey and New York, have developed reference values or criteria for *n*-hexane. The State of New York (for their Short-term Guideline Concentration, SGC, of 42,000 $\mu g/m^3$) and the Commonwealth of Massachusetts (for their Threshold Effects Exposure Limit, TEL, of 47.62 $\mu g/m^3$) based their criteria on occupational exposure limits. The Commonwealth of Massachusetts has developed criteria for alkanes/alkenes in general, and assumed a mixture of equal parts *n*-pentane, *n*–hexane, *n*-heptane and *n*-octane; *n*-hexane as a constituent should not exceed 25% by proportion (MDEP, 1994).

Table 1. Summary of Existing Air Quality Guidelines[1] for *n*-Hexane

Agency	Guideline Value	Basis of Guideline	Date[2]	Comments
US EPA (IRIS)	No ambient air exposure limits are available.			
	RfC (Reference Concentration): 200 µg/m^3.	Epidemiological study of neurotoxic effects in humans.	1990	No air guideline promulgated.
California	Proposed chronic inhalation REL (Reference Exposure Level) : 200 µg/m^3.	RfC from US EPA	1997	*n*-hexane is identified on the June 1996 Toxic Air Contaminant Identification List
Massachusetts	TEL (Threshold Effects Exposure Limits): none for *n*-hexane only; 95.24 µg/m^3(24-hour average) for alkanes/alkenes.	REL-TWA from NIOSH.	1995	Adjusted to allow for exposures via other media.
	AAL (Allowable Ambient Limit): none for *n*-hexane only; 47.62 µg/m^3(annual average) for alkanes/alkenes.	REL-TWA from NIOSH.	1995	Both the TEL and AAL are for Alkanes/Alkenes mixtures, of which *n*-hexane may not exceed 25% by proportion.
Michigan	ITSL (Initial Threshold Screening Level): 200 µg/m^3 (24-hour average).	RfC from US EPA.	1997	Permitting standard, i.e., the Predicted Ambient Impact of a toxic from any facility cannot exceed its screening level.
New Jersey	RfC: 200 µg/m^3 (annual average)	RfC from US EPA.	1994	Permitting application. The RfC must be used in the risk assessments conducted as part of a permit application.
New York State	SGC (Short-term Guideline Concentration): 42,000 µg/m^3 (1-hour average).	TLV-TWA from ACGIH.	1991	Used for permitting.
	AGC (Annual Guideline Concentration): 200 µg/m^3.	RfC from US EPA.	1995	Used for permitting.
WHO	None.			
Netherlands	None.			
Sweden	None.			
CEPA	None.			
Ontario	half-hour POI guideline: 35,000 µg/m^3. 24-hour AAQC: 12,000 µg/m^3.	Both the POI and AAQC are based on health.	1976	Current Ontario air quality standards

1. Guidelines in this table can refer to: guidelines, risk-specific concentrations based on cancer potencies, and non-cancer-based reference concentrations.
2. Date here refers to when the health-based guideline background report or the original legislative initiative was issued. The sources were the respective agency documents. For the US EPA, date refers to when the latest review of the RfC was conducted, if applicable, or the date the IRIS database was accessed, in the case where no RfC has been developed.

The US EPA has developed a Reference Concentration (RfC) for *n*-hexane of 200 μg/m^3. This RfC is based on an epidemiological study by Sanagi et al. (1980) of neurotoxic effects (functional impairment of the peripheral nervous system in several test items) in humans in occupational settings. Michigan, New Jersey and New York adopted the RfC from the US EPA. The California Environmental Protection Agency has also recently proposed to adopt the RfC of the US EPA for its chronic inhalation REL (200 μg/m^3) (OEHHA, 1997). The Commonwealth of Massachusetts derived its annual average Allowable Ambient Limit (AAL) of 47.62 μg/m^3 for mixtures of alkanes and alkenes, based on occupational exposure limits.

4.2 Evaluation of Existing Criteria

The states of New York and Massachusetts base their short term criteria on occupational exposure limits. New York's Short-Term Guideline Concentration is based on the ACGIH TLV-TWA limit for *n*-hexane of 50 ppm (176 mg/m^3) divided by 4.2 to extrapolate to continuous exposures. The Massachusetts 24 hour criterion, is derived for alkanes/alkenes as a group. They are based on the NIOSH REL-TWA for alkane/alkene compounds, including petroleum distillates, *n*-pentane, *n*–octane, and Stoddard Solvent, of 350 mg/m^3 (NIOSH, 1988). For the purpose of air guidelines, the Massachusetts Department of Environmental Protection (MDEP) assumed a mixture of equal parts *n*-pentane, *n*-hexane, *n*-heptane and *n*-octane (MDEP, 1994).

The ACGIH and NIOSH have committees that review the human and animal toxicological responses for a substance, and make recommendations regarding the TLVs and RELs, respectively. The documentation available in support of these recommendations provides a summary of available toxicological data, particularly as it relates to occupational exposures. The method of extrapolation from the toxicological data to the TLV or REL is not clearly outlined and may incorporate a number of policy-related judgements.

The US EPA (1998) has calculated an RfC of 0.2 mg/m^3 (200 μg/m^3) for *n*-hexane. This RfC is based on an epidemiological study of neurotoxic effects (functional impairment of the peripheral nervous system in several test parameters) in humans in occupational settings. The US EPA (1998) cited two critical studies for establishing the RfC. They include; a human epidemiological study examining the neurotoxic effects of *n*-hexane (Sanagi *et al.*, 1980), and a mouse inhalation toxicity study for the adverse effect of *n*-hexane of the nasal cavity epithelium (Dunnick *et al.*, 1989[2]). The RfC for *n*-hexane was based on the human data derived from the study of Sanagi *et al.* (1980). The study of Dunnick *et al.* (1989) identified a NOAEL (no-observed-adverse-effect-level) and a lowest-observed-adverse-effect-level (LOAEL), both of

[2] For a full discussion of the Dunnick *et al.* (1989) study, please refer to the Agency Specific Summary in Section 9.1, Federal Government of the United States.

which were based on mild inflammatory lesions of the nasal epithelium of mice[3]. The value of the LOAEL (human-equivalent-concentration) derived from this animal study, supports the LOAEL of the study of Sanagi *et al.* (1980), in which a NOAEL could not be derived. Furthermore, the data from the tungsten carbide alloy workers (Sanagi, *et al.*, 1980), provides considerable and compelling evidence that *n*-hexane is neurotoxic to humans.

Sanagi et al. (1980) carried out an epidemiological study on two age-matched groups of workers of a tungsten carbide alloy factory. This study investigated the neurotoxicity of *n*-hexane. There were no neurological abnormalities observed. However, neurophysiological tests indicated that the exposed group exhibited significantly reduced mean motor nerve conduction velocities when compared to the control group. Other indices of neurological effects (e.g. slowed residual latency of motor nerve conduction) were significantly different in the exposed group when compared to the control group. These observations were consistent with the *n*-hexane-induced peripheral neuropathy observed in other studies in humans and animals (as reviewed in US EPA, 1998). The Sanagi et al. (1980) study identified the LOAEL for neurological effects as 58 ppm (204 mg/m^3). This LOAEL was based on an eight-hour time weighted average for occupational exposure and was adjusted to a value of 73 mg/m^3 for continuous exposure in the general population. The workers at this tungsten carbide alloy factory were also exposed to acetone concurrently with *n*-hexane. However, the effects of acetone exposure were not considered since there was an absence of evidence to suggest that acetone was toxic to the peripheral nervous system (Sanagi *et al.*, 1980).

An uncertainty factor (UF) of 300 was applied to the adjusted LOAEL derived from the Sanagi *et al.* (1980) study. The factor of 300 is comprised of factors to, protect sensitive individual (UF=10), account for the use of a LOAEL rather than a NOAEL (UF=10), and an additional factor of 3 is to account for the lack of data on reproductive and chronic respiratory effects (US EPA, 1998). Therefore, the RfC is equal to the adjusted Sanagi *et al.* (1980) LOAEL of 73 mg/m^3 divided by the uncertainty factor of 300, resulting in an RfC of 0.243 mg/m^3, which the US EPA rounded down to 0.2 mg/m^3. The US EPA (1998) gives an overall confidence rating of medium to the RfC. The key study is given a medium confidence since the LOAEL in this study (Sanagi *et al.*, 1980) is based on neurotoxicity and this endpoint is supported by numerous other subchronic inhalation studies in animals and by human occupational studies. The database is given a medium confidence because there is a lack of appropriate reproductive studies and long-term inhalation studies.

The States of Michigan, New Jersey and New York (for its Annual Guideline Concentration) have promulgated air quality guidelines or reference concentrations for *n*-hexane by direct

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[3] Adverse effects (mild inflammatory lesions of the nasal epithelium) appear to have been identified at 315 mg/m^3 (the reported NOAEL for this study). This raises questions concerning the identification of this dose level as a NOAEL, and, therefore, calls into question the identified LOAEL (629 mg/m^3).

adoption of the US EPA's RfC. The California Environmental Protection Agency has recently proposed to adopt the RfC of the US EPA for its chronic inhalation REL (200 µg/m^3) (OEHHA, 1997). This value is also based on the US EPA's RfC for the neurotoxic effect of *n*-hexane and alterations in the electrophysiology induced by this agent in humans (OEHHA, 1997).

The World Health Organization, the Netherlands, Sweden and the Canadian Federal government have not established air quality criteria for *n*-hexane.

5.0 Responses of Stakeholders to the Information Draft and the Initial Proposal

5.1 Stakeholder Comments to the Information Draft

In January 1999, the Ministry posted, to the Environmental Registry, information draft documents for eighteen chemicals, including *n*-hexane, for air quality standards development under the Standards Plan (MOEE, 1996; MOE 1999). The Ministry requested input regarding the completeness of relevant inhalation toxicological information examined by the Ministry; the rationale of the agencies that the Ministry has considered appropriate for the development of air quality standards, and technical and economic impacts that may be anticipated as a consequence of the potential revision(s) of the air quality standard.

During the consultation period the Ministry received four submissions from various stakeholders regarding the draft document for *n*-hexane. Stakeholders in the automotive manufacturing industry suggested that the Ministry set a health-based AAQC of 600 µg/m^3 and a POI limit of 1,800 µg/m^3. It was also indicated that their facilities were operating at levels less than 1% of the current standard, recognizing however, that not all industries in Ontario can meet a proposed standard which was derived from the RfC of the US EPA and therefore a technical and economic analysis is needed. A stakeholder from the automobile equipment and parts industry suggested that the reference concentration derived from the ACGIH is the most appropriate and should be used to derive a standard. A stakeholder in the rubber industry noted that its current POI concentration is less than 10% of the current POI standard, but in two or three years its POI concentration will increase to about 10% of the current POI standard. A petroleum products stakeholder suggested that any significant decrease from the current standard would require a risk management analysis.

5.2 Stakeholder Comments to the Initial Proposal

In February 2000, the Ministry posted a proposal for air quality standards for *n*-hexane to the Environmental Registry for a 90-day public consultation period. Five submissions representing the chemical, automobile manufacturing and oil seed processing industries, provided comments focusing on science, policy and risk management issues concerning air quality standard

development for *n*-hexane. Some comments from four industrial stakeholders were of similar nature to those when the preceding Information Draft document was posted on the Environmental Registry. Concerns over the implementation of potentially more stringent air quality standards for *n*-hexane varied among stakeholders of different industrial sectors, the science and science/policy issues surrounding the rationale underlying the proposed air quality standards, however, were similar and these issues are discussed in Section 7.0 of this document.

6.0 Overview of the next Phase of the Ministry's Standards Setting Process

The stakeholders' comments received during the first phase of the standards development process (Information Drafts) were evaluated and utilized in formulating the recommendations which appear later in this document. This first phase, which represented the opportunity for stakeholders to comment on the toxicological and other scientific information used in the development of the air quality standard is now complete. During this initial phase stakeholders were also encouraged to provide information on technical and/or economic considerations or concerns.

The Ministry is now soliciting comments from stakeholders regarding the proposed AAQC and POI standard which are presented in Section 8.0 below. This is the next phase in the overall process of standards development. The goal of this phase is to arrive at a decision regarding the level of the air quality standard for *n*-hexane. If the proposed standard cannot be met immediately, this phase will be followed by a third phase in which risk management options will be discussed with stakeholders. A risk management phase will involve careful consideration of human and ecosystem health benefits and stakeholder inputs regarding the economic impacts and technical feasibility of achieving the standard. In the meantime, the Ministry may propose an interim POI standard to ensure continued environmental improvement while the risk management phase proceeds.

7.0 Considerations in the Development of Air Quality Standards for *n*-Hexane

Ontario currently has air quality standards for *n*-hexane. The half-hour POI guideline is 35,000 $\mu g/m^3$ and the 24-hour AAQC is set at 12,000 $\mu g/m^3$. These criteria were established on the basis of the health effects of this compound.

The most well documented toxic effect of *n*-hexane appears to be its toxicity in the peripheral nerves of humans. In animals, particularly rats, the peripheral and central nervous systems and the male reproductive system appear to be the major target organs. In either case, the metabolite 2,5-hexanedione has been suggested to be the toxic agent. Case studies of occupational exposure to *n*-hexane show that exposures for intermediate (15 to 365 days) and long (over one year)

periods of time result in peripheral neuropathy (degeneration of nerve endings) in humans. The ATSDR has established a minimum risk level for chronic inhalation exposure of 0.6 ppm or 2,100 $\mu g/m^3$. This was derived from a study of workers exposed to approximately 58 ppm (210,000 $\mu g/m^3$) for an average of 6 years.

Available toxicological data does not suggest that *n*-hexane is a significant developmental toxicant, a teratogen, or a genotoxic agent. There are insufficient data to evaluate the carcinogenicity of *n*-hexane. It has been suggested that exposure to other common solvents, such as methyl ethyl ketone, methylisobutyl ketone and toluene, increases the toxicity of *n*-hexane. Since MEK is a common component of solvent mixtures in industrial uses, the effect of MEK may need consideration in *n*-hexane criteria development.

To derive its Reference Concentration (RfC), the US EPA used the adjusted LOAEL of 73,000 $\mu g/m^3$ obtained from the study of Sanagi *et al.* (1980). This agency applied an uncertainty factor of 300 to this LOAEL to obtain a RfC of 200 $\mu g/m^3$. Four U.S. State agencies have adopted this RfC for their air quality guidelines. In the initial Rationale Document for the proposed air quality standards for *n*-hexane, the Ministry considered the RfC an appropriate basis for the development of air quality standards for Ontario. However, specific comments from stakeholders concerning the science and science/policy necessitate a more in-depth review and evaluation of the use of the US EPA RfC as an basis for standards development. The following provides an evaluation of these concerns and the responses of the Ministry.

The RfC of the US EPA as a basis

The rationale for using the RfC of the US EPA to derive the proposed air quality standards was discussed in the Ministry's initial Rationale Document. Major issues surrounding the RfC, as raised by the stakeholders representing the automobile manufacturing and oil seed processing industries, included the key study used by the US EPA, the toxicity endpoint, the threshold and the uncertainty factors employed in the RfC derivation. Recently, the Science Advisory Board (SAB) of the US EPA has performed a review on RfC listed on the Integrated Risk Information System (IRIS) and provided comments on the RfC for *n*-hexane (SAB, 1998). The Ministry has examined comments of all sources, researched on recent toxicological studies and provided revised recommendations on air quality standards for this compound.

The toxicological endpoint

Sensorimotor polyneuropathy induced by long-term exposure to *n*-hexane has been considered the most sensitive toxicological endpoint by our stakeholders and the SAB, and has been discussed in Section 3.0. Symptoms of peripheral polyneuropathy reported in exposed workers included numbness and weakness of the distal portion of the extremities, development of paresthesia (burning and tinkling feeling) and muscular atrophy in the distal extremities (lower

extremities are usually affected earlier and more severe than the upper extremities). Abnormal electromyography and decreased nerve conduction velocity and distal latency have been noted. Histological changes of primary giant axonal degeneration and secondary demyelination, and paranodal and internodal swellings of axons have been observed. Recovery is dependent on severity of neuropathy and may take from a few months to a few years after exposure is terminated. It has been reported that full recovery of motor nerve polyneuropathy in shoe making workers have been observed 10 years after exposure had ceased whereas complete recovery of sensory nerves from polyneuropathy was not observed. Recovery of nerves in the legs is lower than in the arms. There have been recent case reports that commercial *n*-hexane (50% *n*-hexane as a glue component) may induced Parkinsonism (different from idiopathic Parkinson's disease) in workers, suggesting that *n*-hexane may have a central nervous system effect. The neurotoxic effect of *n*-hexane has been attributable to its metabolite, 2,5-hexanedione. This metabolite has been demonstrated to alter neuronal/glial morphology and affect axonal transport in animal studies. The neurotoxic effect of *n*-hexane is characteristic of this hexacarbon solvent and not shared by similar short-chain hydrocarbon solvents, such as pentane and heptane.

Stakeholders representing the oil seed processing industry and the automobile manufacturing industry have considered the neuropathy effect of *n*-hexane as the appropriate endpoint.

Key study for the RfC

The epidemiological study of Sanagi *et. al.* (1980) has been determined by the US EPA to be the principle study to derive the inhalation RfC. This study reported that workers exposed to a low concentration of *n*-hexane (IRIS duration adjusted concentration of 73 mg/m^3) and acetone in a tungsten carbide alloys facility for an average of 6.2 years demonstrated statistically significant decreases in the mean motor nerve conduction velocities (MMCV) and a slowed residual latency (RL) of motor nerve conduction of the lower extremity, whereas no neurological abnormalities were observed. These alterations are consistent with *n*-hexane-induced peripheral neuropathy reported in other recent human studies (Chang, 1991; Kuwabara, *et al.*, 1993; Chang *et al.*, 1993; Smith and Albers, 1997; Chang *et al.*, 1998; Bogucki and Gluszcz-Zielinska, 1999).

Despite that Sciences International Inc. (consultant hired by the oil seed processing stakeholders) claimed that the Sanagi *et al.* (1980) study is out-of-date and not appropriate to be used to derive the RfC, this consultant has concluded that based on science, this principle study is "the most suitable epidemiological study upon which to base an effect for development of an inhalation RfC". Including the study of Sanagi *et al.* (1980), Sciences International has reviewed a total of five epidemiological studies and found that common confounding factors exist within all these studies, such as inadequate sampling of the workplace air and co-exposure to complex hydrocarbon solvents which contained neurotoxic compounds other than *n*-hexane, such as methylethyl ketone (MEK), xylene and toluene. The Sanagi *et al.* (1980) study reported exposure primarily to *n*-hexane and acetone, not to other complex solvents, and there is no

mention of dermal exposure or air measurement problems. However, in view of the small magnitude of the observed effects in motor conduction velocity and the residual latency in nerve conduction, Sciences International is suggesting to consider that this principle study has established a NOAEL, rather than a LOAEL.

Stakeholders representing the automobile manufacturing industry also accept the Sanagi *et al.* (1980) study as the principle study.

Threshold for neuropathy in principle study

Polyneuropathy in workers may occur at low *n*-hexane exposure concentrations (10 - 100 mg/m^3 or 2.8 - 28 ppm) (Wang *et al.*, 1986; Barregard *et al.*, 1991). In the study of Sanagi *et al.* (1980), neurological and neurophysiological examinations were performed on age-matched groups of *n*-hexane-exposed and controlled workers from a tungsten-carbide alloys factory. The 8-hour time-weighted average of *n*-hexane concentration in the exposure environment was 58 ± 41 (mean ± S.D.) ppm or 240 ± 144 mg/m^3. No signs of *n*-hexane exposure related damages to the nervous system in the individual workers were observed. However, taken as a group, the exposed workers showed a minor partiality for functional impairment of the peripheral nervous system in many tests. Statistically significant differences were observed in 1) persistent or transient symptoms regarding muscle weakness and dysesthesia, 2) jump test on one foot, 3) tuning fork test for vibration sensation on the radial process and 4) maximal velocity and residual latency of motor nerve conduction of the posterior tibial nerve.

Sciences International argued that the loss of vibration sensation may be attributed to the noise and vibration of the ball mills at the plant, rather than exposure to *n*-hexane at the low concentrations indicated in this study. Of more interest is the result of the neurophysiological tests. Sciences International explained that the decreases in the mean motor nerve conduction velocities (MMCV) and the slowed residual latency (RL) of motor nerve conduction of the lower extremity (posterior tibial nerve) do not achieve a statistically significant level if the decreases in MMCV and RL are considered one highly related event of nerve conduction and a multiple comparison statistical test was used to analyze the many electrophysiological test results together. Similarly, if the neurological test results were analyzed using the multiple comparison method, the degree of significance in muscle strength, vibration sensation, dysesthesia and headache may decrease.

Sciences International also indicates that the electrophysiological results were inconsistent with other nerve stimulation tests of *n*-hexane exposure studies in that the decrement in tibial nerve conduction velocity was not accompanied by corresponding deficits in ulnar and median nerves of the upper extremity. In addition, the magnitudes of the reported nerve conduction velocity and latency decrement in the Sanagi *et at.* (1980) are small and the within-sample variability is large and therefore, the difference may be a result of random occurrence or outliers in the data.

The Science Advisory Board of the US EPA also questioned the biological significance of the decrease in motor conduction velocity reported by Sanagi *et al.* (1980) and explained that the decrement was a less than 5 % change (SAB, 1998). Most agencies consider a less than 5 % change is biologically insignificant, for example, a TC_{05} (Tolerable Concentration) by Health Canada and a BMC_{05} (bench mark concentration) by the State of California; the US EPA recommends a BMC_{10} approach. Both Sciences International and the Science Advisory Board recommend that the LOAEL of the Sanagi *et al.* (1980) be considered a NOAEL.

Reproductive and chronic studies

The US EPA applied an uncertainty factor of 3 for the lack of reproductive and chronic studies to derive the RfC. The Science Advisory Board of the US EPA, Sciences International (for the oil seed processing stakeholders) and the stakeholders of the automobile manufacturing industry all indicate that both reproductive and chronic exposure studies and data are available and this uncertainty factor of 3 is not valid.

Literature research provided by the oil seed processing and automobile manufacturing stakeholders indicates that there are more recent subchronic/chronic and reproductive/developmental studies performed under Section 4 Test Rule of the Toxic Substances Control Act of the US EPA (cited in TPH Working Group, 1997). These studies investigated effects of exposure to commercial *n*-hexane (53 % *n*-hexane, 16 % 3-methylpentane, 14 % methylcyclopentane, 12 % 2-methylpentane, 3 % cyclohexane, 1 % 2,3-dimethylbutane, and 1 % several minor compounds) in animals. These reports have provided NOAEL of 3000 ppm (10560 mg/m^3) for increased liver weights (rats and mice) and 9000 ppm (31680 mg/m^3) for the lack of neuropathologic effects (rats) in subchronic exposures; NOAEL of 3000 ppm (10560 mg/m^3) for histological changes in nasal tissues and the larynx (rats) and uterine hyperplasia (mice) in chronic exposures; NOAEL of 3000 ppm (10560 mg/m^3) for liver tumour (mice) and 9000 ppm (31680 mg/m^3) for the lack of oncogenic effects (rats); NOEAL of 9000 ppm (31680 mg/m^3) for the lack of developmental effects (rats and mice) and 3000 ppm (10560 mg/m^3) for maternal toxic effects in these reproductive and developmental studies.

The Science Advisory Board of the US EPA has also commented on the appropriateness of the use of an uncertainty factor of 3 in the RfC derivation regarding the sufficient database for reproductive and chronic studies.

Effects of mix solvents

Potential interaction (potentiation) of *n*-hexane-induced polyneuropathy by other hydrocarbon solvents such as methylethyl ketone, methylisobutyl ketone and methyl *n*-butyl ketone on has been discussed in the Ministry's Rationale document and in the literature of recent studies. The lack of neuropathologic effect of exposure of animals to commercial *n*-hexane described in the

TSCA report may be attributed to the use of commercial hexane solvents which did not contain methylethyl ketone or methyl *n*-butyl ketone. The report of Sciences International also mentioned possible enhancement of *n*-hexane-induced neurotoxicity by simultaneous exposure to methylethyl ketone. Some of the commercial mix solvents of *n*-hexane also contain methylethyl ketone, methylisobutyl ketone, and cyclohexane. The Ministry, in agreement with the automobile manufacturing stakeholders, has considered toxicological studies conducted with commercial *n*-hexane; however, specific attention will be given to the potential interaction of *n*-hexane with other hydrocarbon solvents in the enhancement of the polyneuropathy induced by *n*-hexane.

Averaging time for *n*-hexane air standards

The RfC is appropriate to be used as a daily exposure limit for chronic exposures and is within the recommendation of the US EPA. The Reference Concentration is defined by the USEPA as "...an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious non-cancer effects during a lifetime". The RfC is calculated on the basis of a daily exposure over a 70 year lifetime. Jurisdictions apply Reference Concentrations in a manner consistent with their policies and regulations. Ontario considers the 24-hour AAQC a daily limit for long-term exposures. This approach is also used by some other jurisdictions in North America

8.0 Recommendations

The Ministry of the Environment has reviewed and considered air quality guidelines and standards used by leading agencies world-wide. Of the criteria reviewed, the Ministry has evaluated and accepted the scientific studies which support the development of the RfC established by the US EPA. However, following the recommendations by stakeholders, the Ministry has re-evaluated the toxicological information of *n*-hexane provided by these stakeholders and from a research of recent literature, and has also reviewed the comments provided by the Science Advisor Board on the RfC for this compound, the Ministry considers the uncertainty factors used by the US EPA to derive the RfC of 200 $\mu g/m^3$ may not be the most reasonable. The Ministry has summarized the assessment in the following:

- the Sanagi *et al.* (1980) study remains to be the principle study and polyneuropathy is the most sensitive endpoint;
- the uncertainty factor of 10 for individual variability is maintained;
- the study LOAEL is considered a NOAEL and the uncertainty factor of 10 for the extrapolation of a LOAEL to a NOAEL is removed;

- the uncertainty factor of 3 for the lack of reproductive and chronic studies is not considered valid;
- as a precautionary approach, potential interaction with other hydrocarbon solvents remains to be a concern with commercial *n*-hexane.

It is reasonable to derive a 24-hour AAQC for *n*-hexane based on the RfC derivation method of the US EPA with the following adjustment:

AAQC = revised $NOAEL_{(HEC)}$ 73,000 $\mu g/m^3$ / 10 / 3 = 2433 $\mu g/m^3$ or 2,500 $\mu g/m^3$

where 73,000 $\mu g/m^3$ is the revised $NOAEL_{(HEC)}$ based on the $LOAEL_{(HEC)}$ of 73 mg/m^3 of the US EPA; 10 is for the individual sensitivity; 3 is for potential interaction with other hydrocarbon solvents in commercial *n*-hexane.

A Point of Impingement standard of 7,500 $\mu g/m^3$ can be derived from the 24-hour AAQC according to the Ministry's averaging time derivation method (MOE, 1987; MOEE, 1994b).

The Ministry recommends the following AAQC and POI standard for *n*-hexane:

- **2,500 $\mu g/m^3$ (microgramme per cubic metre of air; 24-hour averaging time) based on health effects;**

- **7,500 $\mu g/m^3$ (half-hour averaging time) based on health effects.**

As a final note, case reports of recent human studies indicate that exposure to low concentrations of *n*-hexane (concentrations around or far below the 58 ppm described in the Sanagi *et al.*, 1980 study) has induced polyneuropathy in workers. If sufficient data are available for a more in depth risk assessment for *n*-hexane, the risk-threshold for the air quality standards for this compound may be revised to a level to ensure sufficient health protection.

Considering the magnitude of the reduction from the current POI guideline of 35,000 $\mu g/m^3$ to this revised level of 7,500 $\mu g/m^3$, meeting this proposed POI standard immediately may not be possible due to implementation issues related to economic/technical feasibility and the required timeframe to establish appropriate emission control technology. This consideration is based on an assessment of the known releases of *n*-hexane in Ontario, the environmental levels of *n*-hexane measured in Ontario and on the comments received from stakeholders. Further comments from stakeholders are welcome on the revision of the proposed air quality standards and the implementation issues. The Ministry is currently undergoing stakeholder consultation in the discussion paper "A Proposed Risk Management Framework for the Air Standard Setting Process in Ontario". The risk management framework addresses implementation timeframes for

adopting final effects based air standards (POIs and effects-based air standards with appropriate averaging times) as well as technology and economic issues linked to the introduction of new or revised air quality standards and the introduction of new dispersion models into Ontario's regulatory framework. Consultation is also underway in the discussion paper entitled: "Updating Ontario's Air Dispersion Models".

9.0 A Guide for Stakeholders Responding to this Posting

The Ministry welcomes comments on this proposal from all interested parties. Stakeholders are encouraged to provide comments which indicate whether they support or disagree with the above recommendations. It is also important that submissions from stakeholders include the rationale and reasoning supporting their stated positions so that the Ministry can make informed decisions on the proposed standard on the basis of clear, supportable arguments. The information provided in the submissions will undergo a preliminary risk management analysis within the Ministry in order to determine whether there are compelling implementation issues associated with the standard. If there are, it is likely that a more detailed risk management process will be needed. In the absence of specific, significant implementation issues the Ministry will proceed to finalize the proposed standards.

In order to demonstrate significant implementation issues such as economic impacts and/or technical difficulties in meeting the proposed standard, in the near term, a submission from a company subject to the standard should include the following information:

1. The operations or processes which give rise to emissions of the substance(s) under review;

2. The reduction in emissions that would be required to bring the facility into compliance with the proposed standard;

3. Changes in equipment, potential additional systems or operations (including pollution prevention measures) necessary to achieve and maintain compliance with the proposed standard; including

    - projected capital and annual operating costs of such changes
    - timing
    - any gains in productivity, recovered materials or reduced energy or raw material usage

4. If it is claimed that a standard is not technically achievable, provide documentation of the conditions or circumstances that confirms this position.

5. Provide documentation as to the degree of reduction in emission and ground-level concentration that could be achieved in the operation, facility and/or firm, where compliance with the proposed standard is considered.

In addition, where it is determined that a proposed standard cannot be achieved immediately, please indicate the earliest possible time frame for compliance with the standard.

During discussion with stakeholders regarding air quality standards, the matter of dispersion models used to estimate air quality concentrations at point of impingement has been raised. Currently, O. Reg. 346 states that: "The concentration of a contaminant at a point of impingement ***may*** by calculated in accordance with the Appendix" Section 5(2). The Appendix to Reg 346 outlines three air dispersion models that may be used depending on the site-specific circumstances. Although in the majority of cases the Ministry uses the existing Reg 346 models, there have been instances where other models, such as US EPA's Industrial Source Complex (ISC3), have been used on a site-specific basis.

The Ministry intends to undertake future discussion on the introduction of newer models into policy and regulation, including the United States Environmental Protection Agency's (US EPA) ISC suite of models and the proposed AERMOD model. The introduction of new models will likely influence all other Ministry air quality standards and guidelines as well as the substance addressed in this posting. To this end, the Ministry acknowledges that, if stakeholders make their comments on this substance based on the current use of the air dispersion models, any changes in the models may lead to changes in stakeholders opinions and comments.

The Ministry also appreciates that responding firms may be committed to, or involved in, developing emission reduction strategies under the federal Strategic Options Processes. Please advise the Ministry, in your submission, whether you are a participant in a Strategic Options Process with the federal government that could result in reductions in the use and/or release of this substance from your operations, facility and/or firm. If so, please identify how these anticipated emission reductions, will affect predicted Ground Level Concentrations from your facilities under the existing model.

The foregoing is provided as guidance on the type of information that would assist the Ministry in its ongoing analysis and decision-making in setting an air standard for this substance. In some cases, where it is not feasible to provide all of the information noted within the comment period, the Ministry would appreciate the respondent addressing as many of the issues as possible to ensure an informed decision is made. If stakeholders make no comments about the proposed

standards, it will be presumed that they have no concerns or will have no difficulty, technically or financially, in complying with the proposed standard.

In addition to the general guidance above, the following Ministry documents provide more detail regarding the type of information that would be considered by the Ministry in its standard setting process:

- The Guidance document, *"Procedure for Preparing an Emission Summary and Dispersion Modelling Report - June 1998"* may assist you in completing the air emissions compliance assessment with the proposed air standard;

- MOE *Guideline F-14 (formerly 02-01), "Economic Analyses of Control Documents on Private Sector Enterprises and Municipal Projects" Economic Services Branch- April 1994*, and;

- *"Framework for the Application of Socio-economic Analyses in Setting Environmental Standards." Economic Integration Task Group, Canadian Council of Ministers of the Environment, 1998. http://www.mbnet.mb.ca/ccme/pdfs/SEFrameENG.pdf*

Comments relevant to the setting of air quality standards for *n*-hexane can be sent to:

Jim Smith
Director, Standards Development Branch
Ontario Ministry of the Environment
135 St. Clair Ave West
Toronto, Ontario
M4V 1P5

Fax: 416 327-2936
e-mail: sdb-ebr@ene.gov.on.ca

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11.0 Appendix: Agency-Specific Reviews of Air Quality Guidelines

11.1 Agency-Specific Summary: Federal Government of the United States

1. *Name of Chemical*: *n*-Hexane (hexane) (CAS# 110-54-3)

2. *Agency*: United States Environmental Protection Agency (US EPA)

3. *Guideline Value(s)*:
The inhalation Reference Concentration (RfC) for *n*-hexane is 0.2 mg/m^3 (200 µg/m^3). No air concentration guidelines exist for *n*-hexane.

4. *Application*:
The US EPA has prepared and maintained a database of health risk and regulatory information. This database is called the Integrated Risk Information System (IRIS) and was developed to provide consistent risk information on chemical substances for use in decision-making and regulatory activities. The values reported in IRIS do not represent guidelines or standards.

5. *Documentation Available*:
US EPA, 1998. Integrated Risk Information System (IRIS) Computerised Database. United States Environmental Protection Agency, Washington DC.

Key Reference(s):
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6. *Peer-Review Process and Public Consultation*:
The US EPA makes use of peer-reviewed scientific literature to assess the hazard and to evaluate the potential dose-response relationship of the chemical under review. The assessment methodology and the chemical-specific information undergo scientific and policy reviews.

7. *Status of Guideline*:
Current.

8. *Key Risk Assessment Considerations*:
The US EPA (1998) has calculated an RfC of 0.2 mg/m^3 (200 µg/m^3) for *n*-hexane. This RfC is based on an epidemiological study of neurotoxic effects (functional impairment of the peripheral nervous system in several test items) in humans in occupational settings. The US EPA chose two critical studies for establishing the RfC, i.e., Sanagi *et al.* (1980) and Dunnick *et al.* (1989). The primary reason described in IRIS for the selection of two critical studies was that a no-observed-adverse-effect-level (NOAEL) could not be derived from the Sanagi *et al.* (1980) study. The Dunnick *et al.* (1989) study identified a NOAEL and a lowest-observed-adverse-effect-level (LOAEL), both of which were based on mild inflammatory lesions of the nasal epithelium of mice[4]. The RfC for *n*-hexane was based on the human data derived from the Sanagi *et al.* (1980) study due to *n*-hexane's well documented human neurotoxic effects (US EPA, 1998).

Sanagi *et al.* (1980) carried out an epidemiological study on two age-matched groups of workers. This study investigated the neurotoxicity of *n*-hexane. Neurophysiological tests indicated that the exposed group exhibited significantly reduced mean motor nerve conduction velocities when compared to the control group. Other indices of neurophysiological effects (e.g. slowed residual latency of motor nerve conduction) were significantly different in the exposed group when compared to the control group. These observations were consistent with other studies in humans and animals (US EPA, 1998 and citations therein). The Sanagi *et al.* (1980) study identified the LOAEL for neurological effects as 58 ppm (204 mg/m^3, assuming 25°C and 760 mm Hg). This LOAEL was based on an eight-hour time weighted average for occupational exposure. When converted to continuous exposure (assuming an occupational minute ventilatory volume of 10 m^3/day and a daily minute ventilatory volume of 20 m^3/day) the study LOAEL is adjusted as follows:

$$\text{Adjusted LOAEL} = 204 \text{ mg/m}^3 \times (10 \text{ m}^3\text{/day} / 20 \text{ m}^3\text{/day}) \times (5 \text{ days}/7 \text{ days})$$
$$= 73 \text{ mg/m}^3 \ (73{,}000 \text{ µg/m}^3)$$

The animal study by Dunnick *et al.* (1989) provided a LOAEL that was similar to the LOAEL identified in the Sanagi *et al.* (1980) study, and also identified a NOAEL. Both the NOAEL and LOAEL reported by Dunnick *et al.* (1989) are based on the effect observed as mild inflammatory lesions of the nasal epithelium of mice (portal-of-entry effects). In the Dunnick *et al.* (1989) study, subchronic inhalation of *n*-hexane was carried out using male and female B6C3F$_1$ mice (10/sex/dose) with dose groups as follows: 0, 500, 1,000, 4,000, and 10,000 ppm (0, 1,762, 3,525, 14,099, and 35,247 mg/m^3, respectively). The exposure duration was six-hours per day, 5 days per week for 13 weeks (duration adjusted exposure calculated as 0, 315, 629, 2,518, and

[4]Adverse effects (mild inflammatory lesions of the nasal epithelium) appear to have been identified at 315 mg/m^3 (the reported NOAEL for this study). This raises questions concerning the identification of this dose level as a NOAEL, and, therefore, calls into question the identified LOAEL (629 mg/m^3). The discussion of Dunnick *et al.* (1989) is included here because the US EPA has named it as one of the two critical studies for the *n*-hexane RfC.

6,294 mg/m^3). An additional group of mice was exposed to 1,000 ppm (3,525 mg/m^3) for 22 hours per day, 5 days per week for 13 weeks (duration adjusted exposure calculated as 2,308 mg/m^3). Toxicity was assessed by examining both behavioral and physiological (e.g. body weight, organ weight, organ tissues, etc.) endpoints of toxicity. Histopathological changes included mild inflammatory, erosive and regenerative lesions in the olfactory and respiratory epithelium of the nasal passages of the mice exposed to 2,308 mg/m^3 and above. Multifocal regeneration and metaplasia in the olfactory epithelium were observed at 3525 mg/m^3. Minimal lesions were observed in the 315 and 629 mg/m^3 groups. Other neurohistopathological evidence of toxicity was observed in 6 of the 8 animals in the 2,309 mg/m^3 group and 6 of the 8 animals in the 6,294 mg/m^3 dose group, but not in 8 of the 10 animals in the control group. This study identified a NOAEL of 315 mg/m^3 based on mild lesions. When adjusted for gas:respiratory effects (a factor of 0.122 derived by extrapolation of the surface area for respiratory tract and minute volume differences between humans and the test animal) the human equivalent NOAEL reported in IRIS is 38 mg/m^3 (38,000 µg/m^3) (US EPA, 1998). The next higher dose group was selected as the LOAEL and adjusted by the same procedure as used for the NOAEL. The human equivalent LOAEL is 629 mg/m^3 x 0.122 = 77 mg/m^3 (77,000 µg/m^3). The human equivalent LOAEL derived from this study was similar to the LOAEL derived from the Sanagi *et al.* (1980) study (73 mg/m^3).

The US EPA (1998) reported that the interpretation of the results from the Dunnick *et al.* study may be limited since neuropathological examinations were not carried out on all the tested dose groups. There were also discrepancies in the scoring system used in the paper to "grade" the presence of lesions. The average grade of the lesions in the LOAEL dose group was reported as "minimal to slight" and the average grade of lesions at the highest dose group ranged from "minimal to moderate". Other studies that examined *n*-hexane exposure did not exhibit a dose-response relationship in the severity or incidence of nasal lesions as presented in Dunnick *et al.* (1989).

An uncertainty factor (UF) of 300 was applied to the LOAEL derived from the Sanagi *et al.* (1980) study. The factor of 300 is comprised of factors to protect sensitive individuals (UF=10), the use of a LOAEL rather than a NOAEL (UF=10) and an additional factor of 3 to account for the lack of data on reproductive and chronic respiratory effects (US EPA, 1998).

Therefore, the RfC is equal to the adjusted LOAEL of 73 mg/m^3 of Sanagi *et al.* (1980) divided by the uncertainty factor of 300, resulting in an RfC of 0.243 mg/m^3 which the US EPA rounded down to 0.2 mg/m^3. The US EPA (1998) gives a confidence rating of medium to the RfC and the data base, since the neurotoxicity endpoint identified in the epidemiological study of Sanagi *et al.* (1980) is supported by numerous other inhalation studies in animals and occupational studies from humans but there is a lack of reproductive and long-term inhalation studies.

The US EPA (1998) gives a confidence rating of medium to the RfC and the database.

9. *Key Risk Management Considerations*:
No information available.

10. *Multimedia Considerations of Guidelines*:
No adjustment for multimedia exposure is considered in the development exposure concentrations for threshold effects or unit risk values for non-threshold effects.

11. *Other Relevant Factors*:
None.

11.2 Agency-Specific Summary: State of California

1. *Name of Chemical:* *n*-Hexane (hexane) (CAS 110-54-3)

2. *Agency:* State of California Office of Environmental Health Hazard Assessment (OEHHA); California EPA, Air Resources Board (ARB); California Air Pollution Control Officers Association (CAPCOA)

3. *Guideline Value(s):*
No risk-based concentration limit has been established for *n*-hexane. Recently, the State of California has been proposing to adopt the RfC of 200 $\mu g/m^3$ from the US EPA for its chronic inhalation Reference Exposure Level for *n*-hexane.

4. *Application:*
The Revised 1992 Risk Assessment Guidelines were developed by CAPCOA to provide guidance for the risk assessment procedures which are to be used for the Air Toxics "Hot Spots" Program. This program is based on the California State law *Air Toxics "Hot Spots" Information and Assessment Act* detailed under the Health and Safety Code, Section 44360 *et seq.*, 1987. This Act requires local Air Pollution Control Districts to identify facilities in their area which will conduct health risk assessments, outline how such assessments should be prepared and detail how the results are to be used in prioritizing substances for needs assessments. These guidelines were prepared to provide a methodology by which consistent risk assessments will be performed, thereby facilitating the comparison and review of such reports. The State does not consider these exposure levels to be legally enforceable air quality guidelines or limit values as they should not be employed outside the scope of the program.

The Toxic Air Contaminant Identification List was compiled by the OEHHA and the ARB as part of the State's Air Toxic Program Assembly Bill (AB)-1807. This draft report presents individual summaries detailing the general exposure and health effects for the 244 substances identified on this list. The summaries are not based upon new California EPA evaluations and do not revise California EPA judgements or polices about the potential for these pollutants to cause harm to human health. Though this document identifies risk-based guidance values which have been established or accepted by the OEHHA, the original documentation for such values should be consulted in order to review the conditions under which these values should be reviewed, interpreted and applied.

5. *Documentation Available:*
CAPCOA, 1993. Air Toxics "Hot Spots" Program. Revised 1992 Risk Assessment Guidelines. Toxics Committee of the California Air Pollution Control Officers Association.

ARB, 1996. Toxic Air Contaminant Identification List - Summaries (Draft Report). California Environmental Protection Agency - Air Resources Board. Pages 565-568.

OEHHA, 1997. Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, California, USA.

6. *Peer-Review Process and Public Consultation*:
The Draft Toxic Air Contaminant Identification List is currently undergoing an extensive peer-review and is open for public review and comments. The sources which were used to compile the technical summaries for the 244 substances identified on the Toxic Air Contaminants Identification List were taken from existing governmental exposure and health effects databases (eg., HSDB, IRIS, etc.) and additional widely recognised reference texts.

The RfCs, Reference Exposure Levels (RELs) and cancer potency values reported in both the draft Toxic Air Contaminant Identification List and the CAPCOA documents were prepared and/or adopted for consideration by the OEHHA after extensive review. The rationales for the derivation of all of these values have undergone public review and consultation. Any risk assessment conducted under these guidelines is subject to review by the local district and the OEHHA. In addition, public input plays a key role in the identification and prioritisation of the areas and facilities for which risk assessments are required.

7. *Status of Guideline*:
Not applicable.

8. *Key Risk Assessment Considerations*:
Proposition 65 Safe Drinking Water and Toxic Enforcement Act was issued in 1986 by the California Environmental Protection Agency. This Act details the current status of daily intake levels which have been derived or adopted for carcinogens and reproductive toxicants identified by the OEHHA (ARB, 1996). California has not set a daily intake value for *n*-hexane. The State understands and identifies that the US EPA has established a RfC of 200 $\mu g/m^3$ based on neurotoxicity and nasal epithelial lesions in humans (ARB, 1996). Though this is recognised by the State, *n*-hexane is not listed under Proposition 65 for the lack of activity as a reproductive or developmental toxicant, or as a carcinogen (ARB, 1996). Recently, The State of California has reconsidered the RfC of 200 $\mu g/m^3$ of the US EPA and proposed to adopt this value for its chronic inhalation Reference Exposure Level (OEHHA, 1997).

n-Hexane is listed on the June 1996 Toxic Air Contaminants Identification List (ARB, 1997) for further assessment.

9. *Key Risk Management Considerations*:
Not applicable.

10. *Multimedia Considerations of Guidelines*:
The State of California requires risk assessments to consider exposure to certain substances via non-inhalation pathways (specific compounds are listed under Table III-5 in CAPCOA, 1993). *n*-Hexane is not one of these substances.

11. *Other Relevant Factors*:
n-Hexane is identified by CAPCOA as a quantifiable and reportable substance in any risk assessment undertaken by a facility posting emissions and/or any risk assessment which is required under the "Hot Spots" Program.

11.3 Agency-Specific Summary: Commonwealth of Massachusetts

1. *Name of Chemical*: *n*-Hexane (hexane) (CAS# 110-54-3)

2. *Agency*: Commonwealth of Massachusetts, Department of Environmental Protection (MDEP)

3. *Guideline Value(s)*:
No Threshold Effects Exposure Limit (TEL) exists for *n*-hexane. However, a TEL exists for "Alkanes/Alkenes" mixtures, of which *n*-hexane may be a constituent and is not to exceed 25% by proportion. The TEL for Alkanes/Alkenes is 95.24 $\mu g/m^3$ (24-hour average) and is based on consideration of threshold effects. No Allowable Ambient Limit (AAL) exists for *n*-hexane. However, an AAL exists for Alkanes/Alkenes mixtures, of which *n*-hexane may not exceed 25% by proportion. The AAL for Alkanes/Alkenes is 47.62 $\mu g/m^3$ (annual average) and is based on consideration of threshold and non-threshold effects.

4. *Application*:
The TEL and AAL guidelines are to be employed in the permitting, compliance and enforcement of the Commonwealth of Massachusetts air quality program. The primary goal of the TELs and AALs developed by MDEP is to protect public health from any air contaminant causing known or potentially deleterious effects. These guidelines were developed without regard to production volume, exposure level, regulatory implication, economic considerations, or control technology issues.

5. *Documentation Available*:
Clement Associates, 1989. Structural Activity Relationships of Alkanes and Alkenes. A report prepared for Air Toxics Hotline. Clement Associates, Inc., Fairfax, Virginia. March 1989.

MDEP, 1990. The Chemical Health Effects Assessment Methodology and the Method to Derive Allowable Ambient Air Limits. Vol. I and II. Commonwealth of Massachusetts, Department of Environmental Protection, Boston, Massachusetts. May 1990.

MDEP, 1994. Memorandum from the Office of Research and Standards dated October 20, 1994. This memorandum outlines a number of revisions to the 1990 Chemical Health Effects Assessment Methodology and the Method to Derive Allowable Ambient Air Limits, Commonwealth of Massachusetts, Department of Environmental Protection, Boston, Massachusetts.

MDEP, 1995. Summary Table of Massachusetts Threshold Effects Exposure Limits (TELs) and Allowable Ambient Limits (AALs) for Ambient Air. Massachusetts Department of Environmental Protection (MDEP), Office of Research and Standards, Boston, Massachusetts. December 1995.

MDEP, (undated). Toxicity scoring worksheets for alkanes to develop the TEL and AAL for the Chemical Health Effects Assessment Methodology and the Method to Derive Allowable Ambient Air Limits.

Key Reference(s):NIOSH, 1988. NIOSH Recommendations for Occupational Safety and Health Standards. US Department of Health and Human Services. Public Health Service. National Institute of Occupational Safety and Health (NIOSH), Centers for Disease Control, Atlanta, Georgia. Morbidity and Mortality Weekly Report. Vol. 37. No. S-7. August 26, 1988.

6. *Peer-Review Process and Public Consultation*:
In the development of the Massachusetts ambient air guidelines, peer-reviewed scientific data and analyses from both public and government sources were used. Toxicological information and exposure limits from the following agencies and programs were reviewed: United States Environmental Protection Agency (US EPA), the International Agency for Research on Cancer (IARC), the American National Toxicology Program (NTP), the National Institute of Occupational Safety and Health (NIOSH), the American Conference of Governmental Industrial Hygienists (ACGIH), and the Occupational Safety and Health Administration (OSHA). Internal and external peer-review and public consultation processes have been carried out since 1982.

7. *Status of Guideline(s)*:
No guideline exists for *n*-hexane. The guideline for Alkanes/Alkenes is current. Guidelines may be updated periodically.

8. *Key Risk Assessment Considerations*:
The MDEP has developed a policy for establishing air limits. The methodology addresses both threshold and non-threshold effects, with the selection of the final AAL based on the most sensitive effect. The process focuses primarily on hazard identification and dose-response assessment.

Threshold Effects
Assuming that a chemical has a threshold for adverse effect(s), occupational limits are used to derive the TEL. Where a reference concentration (RfC) exists for a chemical and is published in the Integrated Risk Information System (IRIS) by the US EPA, the methodology outlined in MDEP (1990) has been adapted (MDEP, 1994) to include the RfC in the derivation of TELs and AALs where appropriate and defensible. In the case of *n*-hexane, an IRIS RfC exists. However, the MDEP adopted an approach for assessing alkanes and alkenes as a group of chemicals sharing generally the same properties, including the mode of toxic action. Therefore, instead of using the IRIS RfC, the occupational limit was used. The Most Appropriate Occupational Limit (MAOL) was based on the NIOSH Recommended Exposure Limit (REL) of 350 mg/m^3, which is generally applied to alkane/alkene compounds including Petroleum Distillates (CAS # 8002-05-9), *n*-pentane (CAS # 109-66-0), *n*-octane (CAS # 111-65-9) and Stoddard Solvent (CAS # 8052-41-3). MDEP identified that these chemicals, as a group, tend to have irritant and narcotic effects and potentially some liver

effects. For the purpose of the air guidelines, the MDEP assumed a mixture of equal parts *n*-pentane, *n*-hexane, *n*-heptane and *n*-octane. The MAOL of 350 mg/m^3 was adjusted by the following factors:

I. divided by 4.2 to account for continuous exposure. This adjusts the occupational exposure limit which considers exposure to occur for 8 hours per day, 5 days per week, to consider continuous exposure.
II. divided by 1.75 to account for differences in sensitivity between adults and children.
III. divided by 10 to account for high-risk groups and other sensitive sub-populations.
IV. divided by 10 to account for the lack of low-level, chronic studies in both animals and humans.

The factor applied to the MAOL to calculate the "adjusted" MAOL is, therefore, 735. The adjusted MAOL is numerically equivalent to 0.4762 mg/m^3 (476.2 $\mu g/m^3$). At this point, another set of uncertainty factors were applied to the adjusted MAOL:

I. divided by 1. The Threshold Effects Uncertainty Factor (TEUF) is an uncertainty factor which accounts for acute, chronic, developmental or reproductive effects that may not have been considered in the health risk assessment of the occupational limit. The MDEP applied a score of 1 for *n*-hexane.
II. divided by 5 to account for exposure through media other than air. This is based on an assumption that ambient air contributes only 20% of the total exposure.

The total uncertainty factor applied to the NIOSH REL is 3675. The TEL was, therefore, calculated as 95.24 $\mu g/m^3$.

Non-Threshold Effects

MDEP has not identified alkane/alkene compounds' carcinogenic or mutagenic potential. The agency has identified that certain conjugated alkenes may have positive scores for structure-activity relationships, and therefore an uncertainty factor of 10 was applied in the derivation of the non-threshold exposure limit (NTEL). Using the adjusted MAOL of 476.2 $\mu g/m^3$ as the starting point, a Non-threshold Effects Uncertainty Factor (NTEUF) of 10 was applied. The NTEL was calculated for Alkane/Alkene compounds as 47.62 $\mu g/m^3$.

Allowable Ambient Limit

The AAL is the lower of the TEL or NTEL. Therefore, the NTEL for Alkane/Alkene compounds of 47.62 $\mu g/m^3$ was adopted as the AAL.

9. *Key Risk Management Considerations*:
The selection of the AAL is based on the most sensitive end point of an adverse health effect. The goal of the process is the protection of human health. For carcinogens, the AAL derived in the MDEP process corresponds to a maximum allowable excess lifetime cancer risk of one in one million (10^{-6}) or less.

The process of derivation of air guidelines does not consider technological, economic or enforcement issues.

10. *Multimedia Considerations of Guidelines*:
A factor of 20% was applied to the adjusted MAOL used as the basis of the TEL guideline to allow for contributions from exposure media other than air. However, the AAL does not consider other sources of exposure.

11. *Other Relevant Factors*:
The TEL and AAL described above is applicable to *n*-hexane exposure if *n*-hexane does not exceed 25% of the mixture of alkanes.

MDEP chose not to develop a specific TEL and AAL for *n*-hexane in consideration of the NIOSH (1977) analysis that "...in most workplace situations, workers will be exposed to a mixture of alkanes rather than to a single alkane isomer. Because similar effects result from acute exposures to *n*-hexane and heptane and adverse effects produced by alkanes tend to increase as the carbon number of the alkane increases, it seems likely that components of an alkane mixture may exert additive toxic effects."

The MDEP reviews its recommended air guideline from time to time, and, in the future, may change the guideline for Alkanes/Alkenes to reflect the existence of the IRIS RfC for *n*-hexane. However, no such review is scheduled for the immediate future (MDEP, 1997).

11.4 Agency-Specific Summary: State of Michigan

1. *Name of Chemical*: *n*-Hexane (hexane) (CAS # 110-54-3)

2. *Agency*: State of Michigan Department of Environmental Quality (DEQ)

3. *Guideline Value(s)*: Initial Threshold Screening Level (ITSL) of 200 $\mu g/m^3$, averaged over 24 hours.

4. *Application*:
Screening levels are used for the implementation of Michigan's Air Toxic Rules (Rules 230-232), which apply to any new or modified process for which an application for a permit to install is required, and which emits a toxic air contaminant (State of Michigan, 1995). There are two basic requirements of the air toxic rules as follows:

i) each source must apply the best available control technology for toxics (T-BACT);
ii) after the application of T-BACT, the Predicted Ambient Impact (PAI) of each toxic air contaminant cannot exceed its screening level.

The PAI of each toxic air contaminant is determined using the maximum hourly emission rate for that substance from the facility applying for a permit. The PAI is determined by application of a dispersion model or screening method in accordance with specific regulatory provisions (set out in R336.1240 or R336.1241, or both), by a screening method using a Dilution Matrix included in R336.1230 (Table 22), or by a screening method approved by the regulatory authority.

Screening levels for each toxic air contaminant are developed by the Air Quality Division of the DEQ and are applied across the state. They are used in evaluating the acceptability of emissions from new and modified sources of toxic air pollutants. The intent is to protect ambient air, but the screening levels are not ambient air standards *per se*. Rather, they are health-based levels which the PAI of emissions from a subject facility cannot exceed. If the PAI exceeds the screening level set for a substance, facility-specific physical or operational changes will be required to reduce emissions in order for a permit to be issued.

5. *Documentation Available*:
State of Michigan, 1997. List of Screening Levels (ITSL, IRSL, and SRSL) for Michigan's Air Toxic Rules. Michigan Department of Environmental Quality, Air Quality Division.

State of Michigan, 1989. Final Report of the Michigan Air Toxics Policy Committee-A Proposed Strategy for Processing Air Quality Permit Applications for New Emission Sources of Toxic Air Pollutants. Michigan Department of Natural Resources.

State of Michigan, 1992. R336.1230 Air Toxics from new and modified sources.

State of Michigan, 1995. Procedures for Developing Screening Levels. Michigan Department of Natural Resources, Air Quality Division.

Key Reference(s):
US EPA, 1998. Integrated Risk Information System (IRIS) Computerised Database. United States Environmental Protection Agency, Washington DC.

6. *Peer-Review Process and Public Consultation*:
Peer-reviewed scientific research data, analyses and evaluations from various sources were employed in the development of the ITSL. Specifically, information from the US EPA's process for the development of reference concentrations (RfCs), upon which the ITSL for *n*-hexane is based, were employed.

7. *Status of Guideline*:
Current.

8. *Key Risk Assessment Considerations*:
The health assessment methodology used by the DEQ for non-carcinogenic compounds involves determination of an ITSL. The ITSL is a regulatory level used in evaluating the acceptability of emissions from new and modified sources of toxic air pollutants. The ITSL is set at some fraction of the observable threshold dose determined in studies using laboratory animals or from humans. The methodology for determining the ITSL is contained in Rule 232.

The ITSL for *n*-hexane was adopted from the RfC developed by the US EPA. The ITSL, which is averaged over 24 hours, equals the inhalation RfC (please refer to Section 5.1, Federal Government of the United States, for details regarding the derivation of the RfC).

9. *Key Risk Management Considerations*:
None.

10. *Multimedia Considerations of Guidelines*:
None.

11. *Other Relevant Factors*:
None.

11.5 Agency-Specific Summary: State of New Jersey

1. *Name of Chemical*: *n*-Hexane (hexane) (CAS # 110-54-3)

2. *Agency*: State of New Jersey Department of Environmental Protection (NJDEP)

3. *Guideline Value(s)*:
The State of New Jersey does not have an air quality standard for *n*-hexane (NJDEP, 1997a). A reference concentration (RfC) of 200 $\mu g/m^3$ was adopted from the United States Environmental Protection Agency's (US EPA's) RfC which is based on neurotoxic effects in humans. This RfC is applied for the purposes of conducting risk assessments under the Air Quality Permitting Program.

4. *Application*:
The Bureau of Air Quality Evaluation (BAQEv) Air Quality Permitting Program (AQPP) requires risks to be assessed in conjunction with applying for an air pollution control pre-construction permit. Risks are assessed either by a risk screening conducted by AQPP staff or by a refined risk assessment completed by the applicant. The approach chosen is based on the type and size of the facility or source. The risk assessment must address any toxic air contaminant declared under the New Jersey Administrative Code Toxic Substances List (7:27-17) or which are listed on the Federal Hazardous Air Pollutants List posted under the *Clean Air Act* (NJDEP, 1994).

5. *Documentation Available*:
NJDEP, 1994a. Technical Manual 1003 - Air Quality Regulation Program Bureau of Air Quality Evaluation: Guidance on Preparing Risk Assessment for Air Contaminant Emissions. New Jersey Department of Environmental Protection, Air Quality Permitting Program, Bureau of Air Quality Evaluation.

NJDEP, 1994b. New Jersey Administrative Code Title 7, Chapter 27, Subchapter 17 - Control and Prohibition of Air Pollution by Toxic Substances.

Key Reference(s):
US EPA, 1998. Integrated Risk Information System (IRIS) Computerized Database. United States Environmental Protection Agency, Washington, D.C.

6. *Peer-Review Process and Public Consultation*:
None.

7. *Status of Guideline*:
Not applicable.

8. *Key Risk Assessment Considerations*:
The US EPA's RfC, adopted by New Jersey as their RfC, should be used in risk assessments to estimate the public health risks for inhalation of *n*-hexane using the following equation:

Hazard Quotient = C / RfC

where: C = maximum annual average ambient air concentration in $\mu g/m^3$
RfC = Inhalation RfC = 200 $\mu g/m^3$

The RfC of 200 $\mu g/m^3$ is adopted from the US EPA's Integrated Risk Information System (IRIS) (please refer to Section 5.1, Federal Government of the United States, for the derivation of the RfC). The maximum annual average ambient air concentrations of pollutants (C) are derived from one of three approaches: an initial risk screening assessment, dispersion modelling or air monitoring programs (NJDEP, 1997b).

Hazard quotients which are less than or equal to one indicate a risk which is considered to be negligible. However, hazard indices which are greater than one represent risks which are of concern to the State, and will be evaluated and managed on a case by case basis.

9. *Key Risk Management Considerations*:
Not applicable.

10. *Multimedia Considerations of Guidelines*:
The risk screening procedure used by the AQPP considers only inhalation exposure. Refined risk assessments conducted by permit applicants consider all likely exposure pathways. For non-carcinogens, reference concentrations (RfCs) must be used for inhalation exposure, and reference doses (RfDs) for oral and dermal exposures. The calculated doses from each route of exposure are summed to yield the total dose.

11. *Other Relevant Factors*:
None.

11.6 Agency-Specific Summary: New York State.

1. *Name of Chemical*: *n*-Hexane (hexane) (CAS# 110-54-3)

2. *Agency*: New York State Department of Environmental Conservation (NYSDEC), Division of Air Resources.

3. *Guideline Value(s)*:
Short-term Guideline Concentration (SGC) for *n*-hexane is 42,000 $\mu g/m^3$ (1-hour average) and the Annual Guideline Concentration (AGC) for *n*-hexane is 200 $\mu g/m^3$.

4. *Application*:
The NYSDEC guidelines for the control of toxic ambient air contaminants is intended primarily for use in the decision-making process of permitting emissions (6NYCRR Parts 200, 201, 212 and 257), and for application of certificates of operation for sources of air contamination. The regulatory process used in NYSDEC provides both short- and long-term guidelines to establish appropriate control requirements under existing statutes. The guidelines have been developed to aid the regulatory decision-making process using scientific data and professional judgement. However, they have not been subjected to the same degree of review as applied to an environmental standard.

5. *Documentation Available*:
NYSDEC, 1991. New York State Air Guide-1. Guidelines for the Control of Toxic Ambient Air Contaminants. Draft. New York State Department of Environmental Conservation, Division of Air Resources, Albany, New York.

NYSDEC, 1997. Letter to Sylvia Miedinger, GlobalTox International Consultants Inc., dated February 5, 1997. Subject: Rationale Documents requested for New York State air quality standards. Author: Thomas Gentile, Chief, Toxic Assessment Section, Bureau of Stationary Sources, Division of Air Resources. New York State Department of Environmental Conservation. Albany, New York.

Key Reference(s):
ACGIH, 1991. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices 1990-1991. American Conference of Governmental Industrial Hygienists Inc., Cincinnati, Ohio.

US EPA, 1998. Integrated Risk Information System (IRIS) Computerised Database. United States Environmental Protection Agency, Washington DC.

6. *Peer-Review Process and Public Consultation*:
Peer-reviewed data and computer models were used in the development of the scientific documents supporting the air guidelines. Scientific and professional judgment were employed in the toxicological assessment of contaminant classification and in the screening model analysis.

There are opportunities for public consultation, including the option to review the guidance used in the development of guidelines under certain circumstances and/or the option to develop an ambient air guideline for a contaminant not listed in the current guidelines.

7. *Status of Guideline(s)*:
Current.

8. *Key Risk Assessment Considerations*:
n-Hexane is classified as a moderate toxicity air contaminant (Table III, Appendix C of NYSDEC, 1991). Moderate toxicity air contaminants are defined as animal oncogens, developmental and reproductive toxicants, genotoxic chemicals and other chemicals posing a health hazard to humans.

The SGC was derived from ACGIH Threshold Limit Value-Time Weighted Average (TLV-TWA) (1991) by dividing the ACGIH TLV-TWA (176 mg/m^3) by 4.2 and rounding up to 42 mg/m^3 (42,000 $\mu g/m^3$). The US EPA's RfC of 0.2 mg/m^3 (200 $\mu g/m^3$) for *n*-hexane was adopted as the AGC (please refer to Section 5.1, Federal Government of the United States, for details regarding the derivation of the RfC).

9. *Key Risk Management Considerations*:
Specific computer models have been identified by the agency for use in impact screening as required in the permitting process.

10. *Multimedia Considerations of Guidelines*:
The NYSDEC guideline considers only human exposure to contaminants in air.

11. *Other Relevant Factors*:
None.

11.7 Agency-Specific Summary: World Health Organization (WHO)

1. *Name of Chemical*: *n*-Hexane (hexane) (CAS # 110-54-3)

2. *Agency*: World Health Organization

3. *Guideline Value(s)*:
None.

4. *Application*:
None.

5. *Documentation Available*:
WHO, 1987. Air Quality Guidelines for Europe. WHO Regional Publications, European Series No. 23. World Health Organization, Regional Office for Europe, Copenhagen, Denmark.

6. *Peer-Review Process and Public Consultation*:
Not applicable.

7. *Status of Guideline*:
Not applicable.

8. *Key Risk Assessment Considerations*:
None.

9. *Key Risk Management Considerations*:
None.

10. *Multimedia Considerations of Guidelines*:
None.

11. *Other Relevant Factors:*
None.

11.8 Agency-Specific Summary: The Netherlands

1. *Name of Chemical*: *n*-Hexane (hexane) (CAS # 110-54-3)

2. *Agency*: Netherlands Ministry of Housing, Spatial Planning and the Environment

3. *Guideline Value(s)*:
n-Hexane is not classified under the Netherlands Emission Regulations. (Netherlands Emission Regulations Staff Office, 1992).

4. *Application*:
These emission regulations are intended for use by all licensing authorities in the Netherlands in order to standardise the rules by which emissions are regulated in conjunction with licensing. These emission standards are to be applied as the maximum permissible emission concentration for different waste gas components on a facility specific basis. They are applied to emissions occurring at each source and at the point from which the waste gases leave the processing unit.

Compounds have been categorised into substance classes based on their respective toxicological profiles. There are four substance categories into which compounds are divided (carcinogens, particulates (general), organic or inorganic particulates, and organic or inorganic matter in gaseous or vaporous forms). The emission standard is based on a mass flow limit which has been established for each substance class derived from the application of best available technology. When the untreated mass flow rate of a substance or a class of substances exceeds the critical mass flow limit established for that class, the standard in question is applied to the total discharge for all sources emitting the compound or compounds in that class. Untreated mass flow is defined as "the mass of a particular single substance or summed masses of substances in the same class emitted per unit of time and before any treatment by means of add-on technology" (Netherlands Emission Regulations Staff Office, 1992).

The environmental quality objectives present effects oriented risk levels which have been established for use in a progressive criteria setting program in the Netherlands. The objective of this program is to reduce the emissions of priority substances to a concentration at which the occurrence of adverse effects are considered to be negligible. This program details a long-term environmental quality objective which establishes a target value below which emissions of priority substances must be maintained. This target value is either set at the naturally occurring background level, or a negligible effects concentration which has been established for that compound based on the available toxicological literature. This progressive approach will require facility-specific emissions to be kept below a limit or guidance value which will eventually be tightened to reach the goal of the target value for the compound in question. These guidance or limit values are either air quality statutory requirements or non statutory regional-specific MIC levels.

5. *Documentation Available*:
Netherlands Emission Regulations Staff Office, 1992. Netherlands Emission Regulations - Air (NeR). Netherlands Emission Regulations Staff Office. Bilthoven, The Netherlands.

Netherlands Ministry of Housing, Spatial Planning and the Environment, 1994. Environmental Quality Objectives in the Netherlands - A review of environmental quality objectives and their policy framework in the Netherlands. Risk Assessment and Environmental Quality Division, Ministry of Housing, Spatial Planning and the Environment. The Hague, The Netherlands.

6. *Peer-review Process and Public Consultation*:
The Netherlands Emission Regulations and the Environmental Quality Objectives documents were not peer-reviewed or released for public comment.

7. *Status of Guideline*:
Current.

8. *Key Risk Assessment Considerations*:
None.

9. *Key Risk Management Considerations*:
These Netherlands Emission Regulations standards do not replace existent binding emission or national air quality legal regulations and/or standards. These standards are only to be used as a guidance for licensing agencies until the Dutch Emission Guidelines for the granting of licences is released under the *Environmental Protection Act*.

10. *Multimedia Considerations of Guidelines*:
None.

11. *Other Relevant Factors*:
None.

11.9 Agency-Specific Summary: Swedish Institute of Environmental Medicine

1. *Name of Chemical*: *n*-Hexane (hexane) (CAS# 110-54-3)

2. *Agency*: Swedish Institute of Environmental Medicine

3. *Guideline Value(s)*:
No guideline available.

4. *Application*:
Air emissions in Sweden are regulated by one of two authorities: i) the regional County Government Boards; or ii) the central authority called the National Licensing Board for Environmental Protection. The guidelines are generally applied to permitting of emissions from industrial, heat and power plants.

5. *Documentation Available*:
Victorin, K., 1993. Health effects of urban air pollutants. Guideline values and conditions in Sweden. Chemosphere 27(9) 1691-1706.

Key Reference(s):
None available.

6. *Peer-Review Process and Public Consultation*:
No Information available.

7. *Status of Guideline*:
Not applicable.

8. *Key Risk Assessment Considerations*:
The Institute of Environmental Medicine has performed a number of health risk evaluations on chemicals found in combustion emissions. In general, the Institute develops air guideline values by taking the lowest-observed-effect-level in humans for that compound and applying a factor of between 100 and 1000. For cancer-causing chemicals, air guidelines may be based on a lifetime cancer risk of 1×10^{-5}.

No assessment has been carried out for *n*-hexane.

9. *Key Risk Management Considerations*:
No information available.

10. *Multimedia Considerations of Guidelines*:
No information available.

11. *Other Relevant Factors*:
None.

11.10 Agency Specific Summary: Federal Government of Canada (CEPA)

1. *Name of Chemical*: *n*-Hexane (hexane) (CAS # 110-54-3)

2. *Agency*: Environment Canada/Health Canada - *Canadian Environmental Protection Act*

. *Guideline Value(s)*:
No guideline has been established. *n*-Hexane is not included in the Priority Substances Lists (PSL1 and PSL2).

4. *Application*:
The *Canadian Environmental Protection Act* (CEPA) requires the federal Ministers of the Environment and Health to prepare and publish a Priority Substances List (PSL) that identifies substances that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" as defined in Section 11 of the Act. The assessment of whether substances are toxic is based on the determination of whether they enter or are likely to enter the Canadian environment in an amount that could lead to exposure of humans or other biota at levels that could cause adverse effects. Substances that are assessed as "toxic" may be placed on Schedule I of the Act and considered for possible development of regulations or guidelines.

5. *Documentation Available*:
Environment Canada, PSL2 Secretariat, 1995. Report of the Ministers' Expert Advisory Panel on the Second Priority Substances List Under the *Canadian Environmental Protection Act* (CEPA). October, 1995.

6. Peer-review Process and Public Consultation:
CEPA underwent comprehensive public consultation and review. PSL documents are based on peer-reviewed literature and are peer-reviewed prior to being released.

7. *Status of Guideline*:
Not applicable.

8. *Key Risk Assessment Considerations*:
Not applicable.

9. *Key Risk Management Considerations*:
Not applicable.

10. *Multimedia Considerations of Guidelines*:
Not applicable.

11. *Other Relevant Factors*:
Not applicable.

12.0 Acronyms, Abbreviations and Definitions

AAL	*Allowable Ambient Level* (Massachusetts)
AAQC	*Ambient Air Quality Criteria* - used by the Ontario Ministry of the Environment to define the potential for causing an adverse effect
ACGIH	*American Conference of Governmental Industrial Hygienists* - a non-governmental organization which establishes occupational safety exposure limits for workers
AGC	*Annual guideline Concentration* (New York State)
ATSDR	*Agency for Toxic Substances and Disease Registry* - an agency of the US Department of Health & Human Services
CAPCOA	*California Air Pollution Control Officers Association*
CAS	*Chemical Abstracts Service* - ascribes a unique, identification (registry) number to each chemical to help clarify multiple listings for the same chemical structure
CEPA	*Canadian Environmental Protection Act*
GLC	*Ground Level Concentration* - the concentration of contaminant predicted by dispersion modelling
HEAST	*Health Effects Assessment Summary Tables* - prepared by US EPA's Office of Health and Environmental Assessment. HEAST contains risk assessment information on chemicals that have undergone reviews, although generally not as extensive as the reviews conduced under IRIS
HEC	*Human Equivalent Concentration*
IARC	*International Agency for Research on Cancer*
IRIS	*Integrated Risk Information System* - a database published by the US EPA containing risk assessment information on a wide range of chemicals
IRSL	*Initial Risk Screening Level* - a limit corresponding to a one in a million lifetime risk of cancer used by Michigan for screening new sources of emissions
ITSL	*Interim Threshold Screening Level* - similar to the IRSL, however, derived from the RfC for non-carcinogens
LC_{50}	The concentration of a substance in the medium (eg., air, water, soil) to which a test species is exposed, that will kill 50% of the population of that given species
LD_{50}	The dose of a substance given to a test species, that will kill 50% of the population of that given species
LOAEL	*Lowest-Observed-Adverse-Effect Level*
LOEL	*Lowest-Observed-Effect Level*
MAC	*Maximum Acceptable Concentration*
MACT	*Maximum Achievable Control Technology*
µg	a microgram, one millionth of a gram
mg	a milligram, one thousandth of a gram
MRL	*Minimal Risk Level* - a term used by ATSDR, which defines a daily exposure [either from an inhalation or oral route] not likely to induce adverse non-carcinogenic effects within a given time period, ie., acute, intermediate, or chronic

MOE	*Ontario Ministry of the Environment*, between 1993 and 1997 known as **MOEE** or Ontario Ministry of Environment and Energy
ng	a nanogram, one billionth of a gram
NIEHS	*National Institute of Environmental Health Sciences* (USA)
NIOSH	*National Institute for Occupational Safety and Health* (an agency of the US Department of Health & Human Services)
NOAEL	*No-Observed-Adverse-Effect Level*
NOEL	*No-Observed-Effect Level*
NPRI	*National Pollutant Release Inventory*
NTP	*National Toxicology Program* (USA)
OEHHA	*Office of Environmental Health Hazard Assessment* (California EPA)
OEL	*Occupational Exposure Level*
OSHA	*Occupational Safety and Health Administration* - a branch of the US Dept of Labour
PEL	*Permissible Exposure Limit* (OSHA air standard)
POI	*Point of Impingement* - used in conjunction with dispersion modelling to define the area in which the maximum ground level concentration (GLC) of a contaminant is predicted to occur
ppb	parts per billion
ppm	parts per million
REL	**Either** '*Reference Exposure Level*' as used by the California EPA which defines the concentration at or below which no adverse health effects are expected in the general population **or** '*Recommended Exposure Limit*' used by both NIOSH and ATSDR
RfC	*Reference Concentration* - an estimate of a daily inhalation exposure not likely to induce deleterious non-cancer health effects during a lifetime
RfD	*Reference Dose* - an estimate of a daily exposure dose not likely to induce adverse health effects during a lifetime
RTECS	*Registry of Toxic Effects of Chemical Substances* - database maintained by NIOSH
SGC	*Short-term Guideline Concentration* (New York State)
STEL	*Short-term Exposure Limit*
TC	*Tolerable Concentration* - used by Health Canada to define the airborne concentration to which a person can be exposed for a lifetime without deleterious effects (for non-carcinogens)
TC_{05}	*Tumorigenic concentration* - the concentration of a contaminant in air generally associated with a 5% increase in incidence or mortality due to tumours
TD_{05}	*Tumorigenic dose* - the total intake of a contaminant generally associated with a 5% increase in incidence or mortality due to tumours
TLV	*Threshold Limit Value* - an exposure concentration that should not induce an adverse effect in a work environment
TWA	*Time-Weighted-Average* - allowable exposure averaged over an 8-hour workday or 40-hour work week
US EPA	*United States Environmental Protection Agency*

WHO *World Health Organization*